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(54) Title: ORAL STEROIDAL HORMONE COMPOSITIONS AND METHODS OF USE

(57) Abstract

Provided are oral dentifrice compositions comprising a therapeutically effective amount of estrogen or an estrogen–containing substance. A variety of different methods of using the compositions, for example in the treatment or prevention of tooth loss or osteoporosis, are also provided. Additionally, therapeutic kits comprising one or more of the present compositions are provided.

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ORAL STEROIDAL HORMONE COMPOSITIONS AND METHODS OF USE

1.0 BACKGROUND OF THE INVENTION

The present patent application claims priority to provisional patent application 60/133,085 filed May 7, 1999.

1.1 FIELD OF THE INVENTION

The present invention relates generally to the fields of medicine and oral health. More particularly, it concerns oral dentrifice compositions that comprise steroidal hormones or derivatives thereof, and methods of using these compositions, for example to provide estrogen to subjects in need of estrogen replacement, or in the treatment or prevention of tooth loss or osteoporosis. Therapeutic kits comprising the compositions are also provided.

1.2 DESCRIPTION OF RELATED ART

Osteoporosis is becoming a growing problem among older women, particularly in the United States. Osteoporosis is diagnosed when bone mineral density decreases to less than 2.5 standard deviations below the young adult peak mean. Osteoporosis, characterized by reduction in bone mineral density to the extent that fractures occur after minimal trauma, is a disease process and not a component of normal aging. The incidence of osteoporosis, extent of patient suffering, and economic costs are quite significant (Ray *et al.*, 1997; Melton *et al.*, 1997; Cooper and Melton, 1992; Cooper *et al.*, 1992). Artificial menopause in women undergoing a hysterectomy and a bilateral oophorectomy (Lepine *et al.*, 1997) also represents an osteoporosis risk. Approximately 600,000 women undergo this procedure each year.

In the body, bone is remodeled continuously through the process of resorption by osteoclasts, followed by bone formation by osteoblasts. Normally, the activity of these two types of cells is balanced through the action of hormones and other signaling mechanisms. During the resorption phase sites for remodeling are targeted by osteoclasts that form pits in bone, releasing organic matrix and minerals into the circulation. Resorption at a single site can last as long as about three weeks. As resorption progresses, osteoblasts begin filling in the resorbed region with new mineralized bone.

Peak bone mass is reached at about age 30. After peak bone mass is reached, there is a gradual age-related loss of bone mass in both males and females due to a slight imbalance in resorption and formation. However, as estrogen production declines in women around the time

of menopause, bone resorption increases dramatically, which can lead to rapid bone loss. Premenopausal women have been shown to turnover bone at a rate of about one-third to one-half gram of bone per day, while the turnover is double to triple that in early postmenopausal women. Although bone loss can be especially elevated in the five to seven years immediately following menopause, this process continues throughout life. The rate of bone loss can vary dramatically from woman to woman.

Several studies have documented this dramatic increase in bone turnover levels at menopause (Ebeling *et al.*, 1996; Garnero *et al.*, 1996a; Prestwood *et al.*, 1994). The results showed that the increase in both the mean and the range of bone resorption values stayed high for more than 20 years beyond menopause, a pattern consistent with bone mass changes over a woman's lifetime. These studies demonstrated an inverse correlation between bone turnover and bone mass, with high turnover associated with low bone mass.

Interventions for preventing and treating bone loss have focused on increased intake of calcium and vitamin D, exercise, smoking cessation, the use of calcitonin, bisphosphonates such as alendronate, SERMs such as raloxifene, and estrogen replacement therapy/hormone replacement therapy (ERT/HRT). Estrogen replacement therapy (ERT) and hormone replacement therapy (HRT) have been shown to be effective in preventing further bone loss by inhibiting osteoclastic activity in the bone remodeling process, thereby reducing bone resorption. In one 3-year study, women who received HRT had increased bone mineral density, whereas those who received placebo did not. The trial demonstrated significant benefits of estrogen therapy in maintaining bone density at the spine. Women who were consistently compliant with their estrogen regimen had a 3.5% to 5% mean total increase in spine bone mineral density; estrogen plus continuous medroxyprogesterone acetate (MPA) resulted in a significantly higher bone mineral density (5%) compared with the other regimens (estrogen alone, estrogen plus cyclic MPA, or estrogen plus cyclic micronized progestin). Similar results were seen at the femoral neck; consistent compliance produced an increase of approximately 2% (PEPI Study Clinicians, 1996a).

The earlier estrogen replacement is begun after menopause, the more protective its effect on bone density (Lindsay, 1987). Results from a 16-year placebo-controlled trial of the effects of estrogen deficiency on bone loss in oophorectomized women found that metacarpal bone mineral content decreased 20% over 15 years in women who did not take estrogen. Conversely, estrogen therapy retarded bone loss regardless of whether treatment began 0, 3, or 6 years postoophorectomy; however, lost bone mass was not replaced and best results were

achieved when estrogen replacement was initiated soon after bilateral oophorectomy. The increase in bone density at the spine increases with the number of years after the menopause (Lindsay and Tohme, 1990). Several case control and cohort studies have also compared the use of estrogen in preventing the risk of hip fractures; the mean relative risk for those who had ever used estrogen was 61%; for current users, it was 45%. Overall, reductions in fracture risk ranged from 20% to 60% (Gallagher, 1996).

However, despite the many documented benefits of estrogen replacement therapy, compliance remains a significant problem. A substantial number of women who are prescribed estrogen either do not fill the prescription or discontinue therapy within less than 5 years. In a study of 685 women who were screened, designated "at risk" for osteoporosis, and given estrogen therapy, only 49% were still taking estrogen at the end of 1 year (Torgerson *et al.*, 1995). The compliance rate was only marginally better in women who had undergone a hysterectomy (59%). Even in prospective clinical trials where women were closely monitored, compliance rates were only in the 80% range (PEPI Study Clinicians, 1995).

Several factors may contribute to the lack of compliance seen in patients undergoing hormone replacement therapy. Among the more common are the side effects of estrogen-containing preparations that cause changes in vaginal bleeding pattern and abnormal withdrawl bleeding or flow, breakthrough bleeding, spotting, increase in size of uterine leiomyomata, vaginal candidiasis, change in amount of cervical secretion, breast tenderness and enlargement and nausea. Less common is a long list of side effects that range from mild discomfort to those of a more serious nature. These include enlargement of benign tumors ("fibroids") of the uterus, retention of excess fluid (this may make some conditions worsen, such as asthma, epilepsy, migraine, heart disease or kidney disease) and spotty darkening of the skin, particularly on the face, vomiting, abdominal cramps, diarrhea, abdominal bloated feeling, cholestatic jaundice, increased incidence of gallbladder disease, chloasma or melasma that may persist when use is discontinued, erythema multiforme, erythema nodosum, hemorrhagic eruption, loss of scalp hair, hirsutism, steepening of corneal curvature, intolerance to contact lenses, headache, migraine, dizziness, mental depression, chorea, increase or decrease in body weight, decrease carbohydrate tolerance, aggravation of porphyria, edema and changes in libido (Physicians' Desk Reference®, 2000).

In attempting to avoid at least some potential side effects, estrogens have been formulated for use in transdermal patches or injectable preparations. Unfortunately, transdermal estradiol preparations have caused skin reactions or irritation at site of application

in 30 to 80% cases, including burning sensation, itching, pain, discomfort, erthycura, and swelling of the skin (Physicians' Desk Reference®, 2000). Vaginally applied estradiol creams may cause excessive vaginal discharge, vulvar and vaginal irritation and discomfort and inconsistent blood absorption (Physicians' Desk Reference®, 2000). Injectable estrogen formulations are even less desirable due in no small part to unpredictable effect and local pain discomfort (Physicians' Desk Reference®, 2000).

By far the most popular form of estrogen therapy is conventional tablet administration. But because of the uncomfortable side effects including cramps, bloating and nausea suffered by many women, compliance is relatively low and contributes to reluctance to continue preventive therapy. Therefore, there is a need for new and effective compositions and methods and uses for hormone replacement therapy, such as estrogen replacement therapy, particularly those that will be well accepted and provide safe and effective alternative route of administration. Well-tolerated formulations would lead to increased compliance, thereby providing more patients with protection from osteoporosis, decreasing urogenital atrophy and reducing hot flashes.

2.0 SUMMARY OF THE INVENTION

The present invention overcomes one or more of these and other shortcomings in the art by providing effective oral dentrifice compositions comprising at least a first steroidal hormone or derivative thereof, exemplified by, but not limited to, estrogens or an estrogen derivatives, progestins or progestin derivatives, testosterones or testosterone derivatives, and a variety of methods of using these compositions including treating or preventing osteoporosis. The compositions may also include other steroid hormones or derivatives thereof, or substances that enhance bone resorption and supplement the effect of the steroidal hormone formulations. The oral dentrifice compositions provided herein have fewer of the side reactions associated with other routes of administration, yet offer the same therapeutic and preventive advantages.

Several terms and phrases are used herein with the following definitions and may be found at various places throughout the specification.

The terms "a" and "an" are used in the sense that they mean "at least one", "at least a first", "one or more" or "a plurality" of the referenced components or steps, except in instances wherein an upper limit is thereafter specifically stated. Therefore, "steroidal hormone or a steroidal hormone derivative", as used herein, means "at least a first steroidal hormone or a

steroidal hormone derivative". The operable limits and parameters of combinations, as with the amounts of any single substance, will be known to those of ordinary skill in the art in light of the present disclosure.

The term "a second" is used in the sense that it means "at least two", "at least a second", "two or more" or "a plurality" of the referenced components or steps, except in instances wherein an upper limit is thereafter specifically stated. Therefore, the phrase "at least a second distinct antiosteoporosis agent" will be understood to include two, more than two or a plurality of distinct antiosteoporosis agent(s) wherein estrogen is the first antiosteoporosis agent. The operable limits and parameters of combinations, as with the amounts of any single agent, will be known to those of ordinary skill in the art in light of the present disclosure.

The phrase "safe and effective amount" is used in the sense that it means an amount of at least a first steroidal hormone or derivative thereof, such as an estrogen or an estrogen derivative, high enough to provide a significant positive modification in the prevention of osteoporosis, but low enough to avoid serious side effects within the scope of sound medical judgment at a reasonable benefit/risk ratio.

The present invention is applicable to all subjects in need of steroidal hormones such as estrogen, progesterone and testosterone, particularly animals, more particularly mammals and even more particularly humans. The present invention is further applicable to valuable or valued animals, such as race-horses, domestic pets, livestock and farm animals that are used to produce food for human consumption. The present invention is applicable to young and old, male and female mammals including, but not limited to, horses, dogs, cats, cows, pigs, boar, sheep, goat, buffalo, bison, llama, deer, elk, calves, lambs, rabbits, hares and humans. The present invention is applicable to humans including, but not limited to, newborns, infants, toddlers, children, adolescents, teenagers, menstrating, perimenopausal and postmenopausal women, men and elderly people. The present invention is also applicable to subjects having or at risk of developing including, but not limited to, decreased bone density, osteoporosis, tooth loss, an steroidal hormone deficiency, infertility or subjects having reproductive or sex organs that do not synthesize and/or secrete steroidal hormones. Further, the present invention is applicable to subjects having or at risk of developing nutrient deficiencies including, but not limited to, calcium, particulary in humans who smoke. The present is further applicable to humans having or at risk for developing sexual dysfuntion. However, in preferred aspects of the invention, the subject is a human subject. In more preferred aspects of the invention, the human subject is a female human subject. In further preferred aspects of the invention the

female human subject is a peri- or postmenopausal woman of about above the age of 45 or a woman with surgical menopause, a menopausal disorder, or premature menopause.

Three major classes of steroidal hormones exist. They are sex hormones, progestins and corticosteroids. Steroid hormones stimulate protein synthesis. As used throughout the entire application, the phrase "steroidal hormone or derivatives thereof" is used in the sense that it includes, but is not limited to, estrogen, an estrogen derivative, an estrogen-containing substance, an estrogen derivative containing substance; progestin, a progestin derivative, a progestin-containing substance, a progestin derivative containing substance; or testosterone, a testosterone derivative, a testosterone containing substance or a testosterone derivative containing substance. It is understood that the oral dentrifice compositions comprisingat least a first steroid hormone or the combinations described herein may include steroidal hormone derivatives, so long as such derivatives function with similar hormonal activity. Synthetic as well as natural forms of the hormones are included. Some examples of steroidal hormones include pregnenolone, progesterone, testosterone, estrone, estradiol, estriol, androsteredione, tetrahydrocorticosterone, cortisol (hydrocortisone), tetrahydrocortisol, 11 α-epihydrocortisol, cortisone, tetrahydrocortisone, corticosterone, 17 α-hydroxyprogesterone, prednisolone, pregnenolone and tetrahydrocortexolone.

The male hormone, testosterone, and the female hormones, estrogens and progesterone, are derived from pregnenolone. Pregnenolone is the precusor of all steroid hormones, which is first derived from cholesterol.

Estrogens are female sex hormones synthesized and secreted by the ovarian follicle. They occur naturally and synthetically in several forms including, but not limited to, conjugated estrogen, esterified estrogen, estradiol, estradiol derivatives, estrone, estrone derivatives, estriol and estriol derivatives. Progesterone is also a female sex hormone, which occurs naturally and is secreted by the ovarian follicle, placenta and adrenal gland. It is responsible for the development of uterine tissues, preparing the tissue lining the uterus for implantation of an ovum and the maintenance of pregnancy.

Testosterone is the male sex hormone essential for normal growth and development of male sex organs, such as the prostate, seminal vesicles, penis and scrotum. It is further required for maintenance of the secondary sex charateritics, for example, the development and distribution of facial, pubic and chest hair.

The present invention provides oral dentrifice compositions comprising a therapeutically effective amount of at least a first steroidal hormone or a steroidal hormone

derivative. In preferred aspects of the invention, the oral dentrifice composition comprises a therapeutically effective amount of at least a first estrogen or an estrogen derivative or an estrogen-containing substance. As used herein, the term "oral dentrifice composition" will be understood to include compositions formulated as a toothpaste, tooth powder, mouth and gum powder, dental cream, prophylaxis paste, mouthwash, mouthrinse, lipid or non-lipid oral gel, lozenge, chewing gum, dental tablet, foaming dental tablet or pastille. Dental floss and toothpicks are not included in the term "oral dentrifice composition" as used herein. In preferred aspects of the present invention, the oral dentrifice composition is formulated as a toothpaste or a mouthwash.

In preferred aspects of the invention, the oral dentrifice composition is formulated as a toothpaste. The oral dentrifice composition is administered to the subject by at least a first brushing of the teeth of the subject, or alternatively by brushing of the teeth of the subject twice per day, three times a week or only once per day, for example, each evening.

The oral dentrifice compositions are formulated to contain a therapeutically effective amount of at least a first estrogen, an estrogen derivative or an estrogen-containing substance. This amount will generally be between about 0.1 mg and 6 mg, preferably, between about 0.2 mg and about 3 mg, and most preferably between about 0.25 mg and about 2.5 mg.

In certain applications, low doses of the therapeutically effective amount of estrogen or an estrogen-containing substance for human administration are desirable and will be about 0.1, 0.15, 0.2, 0.25, 0.3, 0.35, 0.4, 0.45, 0.5, 0.55, 0.6, 0.65, 0.7, 0.75, 0.8, 0.85, 0.9, 0.95, or about 1 mg. In other aspects, higher doses will be necessary to obtain a desired effect and useful high doses of such therapeutically effective amount of estrogen or an estrogen-containing substance for human administration will be about 1.5, 2, 2.5, 3, 3.5 or about 4 mg. Any particular range using any of the foregoing recited exemplary doses or any value intermediate between the particular stated ranges is contemplated and will be encompassed within the present invention. In accordance with conventional formulations, unit doses will refer to amounts that are prepared for single, multiple and sequential use and may include any of the above amounts.

Another preferred embodiment of the present invention is a mouthwash composition. Conventional mouthwash composition components can comprise the carrier for the active agents of the present invention. Mouthwashes generally comprise from about 20:1 to about 2:1 of a water/ethyl alcohol solution and preferably other ingredients such as flavor, sweeteners, humectants and sudsing agents such as those described herein. The humectants, such as

glycerin and sorbitol give a moist feel to the mouth. Generally, a mouthwash or mouthrinse according to this invention may contain, for instance, up to about 20% of ethyl alcohol, about 0% to about 50% of humectant, about 0.1 to 5% of an emulsifying agent (surfactant), about 0% to 0.5% of a sweetening agent, about 0.03% to 0.3% of a flavoring agent.

Accordingly, as used throughout the entire application, the term "unit dose" is used in the sense that it means the amount administered per dosage applied in each administration. Such units may include, but are not limited to, mg, mg/mL, cubic centimeter, g/cm^3 or g/cm^2. It will be understood the units of dosage and the dosage may vary depending on the formulation and the concentrations of the formulation of the oral dentrifice composition.

Examples of oral estrogen compounds include, but are not limited to, conjugated equine estrogens (avalible doses include: 0.3, 0.625, 0.9, 1.25, and 2.5 mg), piperazine estrone sulfate (avalible doses include: 0.3, 0.625, 1.25, 2.5 and 5 mg), estropipate, estradiol valerate (avalible doses include: 1 and 2 mg), estradiol hemisuccinate and micronized estradiol (avalible doses include: 1 and 2 mg). Examples of synthetic estrogen compounds include, but are not limited to, diethylstilbestrol (avalible doses include: 0.1, 0.25, 0.5, 1 and 5 mg), ethinyl estradiol (avalible doses include: 0.02, 0.05 and 0.5 mg), quinestrol (avalible dose: 0.1 mg) and mestranol. Examples of topical vaginal estrogen compounds include, but are not limited to, estropipate, conjugated equine estrogen, dienestgrol and diethylstilbestrol. Examples of topical transdermal estrogen compounds include, but are not limited to, 17β-estradiol (3 days), 17β-estradiol (3.5 days), 17β-estradiol (7 days) and estradiol – vaginal ring. In particular embodiments of the invention, the estrogen-containing substance is selected from the group consisting of conjugated estrogen, an esterified estrogen, estradiol, an estradiol derivative, estrone, an estrone derivative, estriol and an estriol derivative.

The oral dentrifice compositions may additionally comprise one or more of an abrasive or polishing agent, a fluoride ion source, a binder, a humectant, a surfactant or emulsifying agent, a thickening or consistency regulating agent, a chelating agent, a gelling agent, a sudsing agent, a pellicle film penetrating agent, a flavoring agent, a sweetening agent, an anticalculus agent, an antiplaque agent, an antigingivitis agent, a pigment or coloring agent, an antibacterial agent, a whitening agent, a preservative, a stannous salt or water.

In additional aspects of the present invention, the oral dentrifice compositions further comprises a therapeutically effective amount of at least a first progestogen compound, and/or a therapeutically effective amount of at least a second distinct antiosteoporosis agent including, but not limited to, a selective estrogen receptor modulator, such as tamoxifen or raloxifene,

alendronate, calcitonin, caicium, fluoride, risedronate, etridronate, pamidronate, ipriflavone, germanium, vitamin K and vitamin D. In preferred aspects of the present invention, the oral dentrifice compositions further comprise a therapeutically effective amount of at least a first progestogen compound, and/or a therapeutically effective amount of at least a second distinct antiosteoporosis agent selected from the group consisting of selective estrogen receptor modulator, such as tamoxifen or raloxifene, alendronate, calcitonin, calcium, fluoride, and vitamin D. Specific examples of progestin compounds include, but are not limited to, medroxyprogesterone acetate, megestrol acetate, norethindrone (norethisterone), micronized progesterone, norethindrone acatate and norgestron.

The present invention also provides kits comprising, in at least a first suitable container, the oral dentrifice composition comprising a therapeutically effective amount of at least a first steroidal hormone or steroidal hormone derivative and, optionally, a device for administering said composition. Kits will typically contain instructions for use. In preferred aspects of the invention, the steroidal hormone is estrogen, an estrogen derivative, an estrogen-containing substance or an estrogen derivative containing substance.

In terms of compositions, kits and/or medicaments of the invention, the combined effective amounts of the therapeutic agents may be comprised within a single container or container means, or comprised within distinct containers or container means.

There are several forms in which the dentrifice may be formulated such as a mouthwash or toothpaste with toothpaste being particularly preferred. The device for administering is preferably a toothbrush, but may also be a device such as a mouthguard or mouthpiece. As used herein, the terms "mouthguard or mouthpiece" will be understood to include a device useful for administering the present oral dentrifice composition. The device includes a U-shaped mold formed from orally acceptable plastics having a plurality of enclosed cavities or voids therein useful for filling to administer the present oral dentrifice composition by extented contact with a substantial portion of the subjects teeth and gums. Types of toothbrushes that can be used include, but are not limited to, a traditional, soft, medium or hard toothbrush, an electric toothbrush or an ultrasonic toothbrush.

The kits may further comprise at least a first progestin, progestogen, progesterone compound or a derivative thereof, a testosterone compound or derivative thereof, an antiosteoporosis agent or a combination of any one or more of these compounds or agents with the estrogen compound. Instructions for use may also be provided in any of these kits.

It is contemplated that the oral dentrifice compositions will also be useful in providing agents that are effective in activating the enzyme guanylate cyclase, increasing serum levels of cyclic guanosine monophosphate (cGMP), which produces smooth muscle relaxation of the corpus cavernosum and allows inflow of blood, followed by erection of the penis. An exemplary compound is sildenafil citrate, also known as Viagra® (Pfizer, Inc., New York, NY).

Sildenafil citrate is a white crystalline powder. It is soluble in water. Sildenafil Citrate is chemically described as 1-[[3-(6,7-dihy-dro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4-methylpiperazine citrate, having a molecular weight of 666.7.

Three dose preparations that contain 25mg, 50mg and 100mg of sildenafil citrate, respectively, are available.

Further, it will be understood that use of the oral dentrifice composition, preferably formulated as a toothpaste or mouthwash, comprising sildenafil citrate or sildenafil citrate admixed with testosterone by said subject should occur about 4 hours to about one-half hour before sexual activity due to rapid absorption of sildenafil citrate.

It is contemplated that the use of such compositions will overcome any emotional distress, embarrassment or social stigma associated with the administration of an medicinal oral tablet to aid in the correction of sexual dysfunction as well as overcome any possible side effects experienced by subjects who orally ingest the tablet form of sildenafil citrate.

Each of the preceding compositions and combinations thereof are useful in a variety of therapeutic and medicinal embodiments. For example, y and in administering oral dentrifice compositions comprising at least a first steroidal hormone or derivative thereof to a subject in need thereof. Further, each of the preceding compositions and combinations thereof are useful in the manufacture of such. As previously stated, subjects that may be in need of such compositions include, but are not limited to, subjects having or at risk of developing including, but not limited to, decreased bone density, osteoporosis, tooth loss, an steroidal hormone deficiency, infertility, reproductive or sex organs that do not synthesize and/or secrete steroidal hormones, nutrient deficiencies or sexual dysfuntion.

The present invention also provides methods of, and uses in, compensating for a loss of sterodial hormones in a subject, such as a human subject, comprising administering to the subject a biologically effective amount of an oral dentrifice composition comprising a

therapeutically effective amount of at least a first steroidal hormone or steroidal hormone derivative.

Additionally, the invention provide methods of or uses in treating or preventing tooth loss, comprising administering to a subject, such as a human subject, having or at risk of developing tooth loss an effective amount of an oral dentrifice composition comprising a therapeutically effective amount of at least a first estrogen, an estrogen derivative or an estrogen-containing substance.

Testosterone is used to treat hypogonadism, which is a condition that results from insufficient secretion of the male sex hormone. Symptoms of hypogonadism include impotence, decreased libido, fatigue, depression and abnormal secondary sex characteristics. Therefore, testosterone replacement therapy is typically used to treat men having or at risk of having a deficiency or absense of testosterone. Testosterone in combination with female steroidal hormones is also used in women to treat conditions characterized by changes or decreases in libido or the desire for sexual activity. Testosterone combined with estrogen is sometimes used in oral contraceptives and in the treatment of osteoporosis.

Progesterone is used for the treatment of infertility and progesterone deficiency in women. It is also used in combination with estrogen for the treatment of osteoporosis and to reduce the risks associated with the use of estrogen. Such risks include, but are not limited to, incidence of hyperplasia and endometrial cancer.

It is contemplated that the use of oral dentrifice compositions comprising a therapeutically effective amount of at least a first estrogen or an estrogen-containing substance will place the estrogen close to the estrogenic receptor of the jawbone, resulting in estrogen absorption through the buccal and gingival mucosa into the systemic circulation. The estrogen acts on the receptor to prevent jawbone osteoporosis and subsequent tooth loss. It is believed that the new and effective oral dentrifice compositions and methods and uses for estrogen replacement therapy may enchance the local effect on the jawbone thereby increasing its bone mass density and decreasing the tendency of tooth loss. This particular aspect of the invention will allow treatments that focus on prevention of jawbone loss and will not require high blood levels of estrogen. Thus a patient may receive low unit doses of estrogen compounds via an oral dentrifice, maintain relatively low blood levels of the estrogen without running the risk associated with hormone replacement therapy blood levels which affect a subgroup of individuals. In such cases, a benefit of decreasing local bone loss in the jawbone would be achieved without the risk associated with maintaining higher blood levels of the hormone.

The present invention thus provides methods of, and uses in increasing bone density, in at least a first bone of a subject, such as a human subject, comprising administering to the subject a biologically effective amount of an oral dentrifice composition comprising a therapeutically effective amount of at least a first estrogen or an estrogen-containing substance. In preferred aspects of the invention, the at least a first bone is the jaw bone of the subject. In more preferred apects of the invention, the at least a first bone is the jaw bone of a human subject.

In another aspect of this particular use of the invention, the at least a first estrogen or an estrogen-containing substance, may be combination with other therapeutic agents specific for the estrogen receptor and particularly those other therapeutic agents specific for the jawbone estrogen receptor.

Important aspects of the invention are methods of, and uses for, the treatment and/or prevention of osteoporosis in a subject, for example, a human subject, comprising administering to the subject a biologically effective amount of an oral dentrifice composition comprising a therapeutically effective amount of estrogen or an estrogen-containing substance. In preferred aspects of the invention, the subject is a human subject. In more preferred aspects of the invention, the human subject is a female human subject.

The present invention also provides methods of, or uses in, treating or preventing a condition characterized by a dentally localized estrogen deficiency, comprising delivering to the oral cavity a localized effective amount of an oral dentrifice composition comprising a therapeutically effective amount of at least a first estrogen or an estrogen-containing substance.

Concerning all methods, the terms "a" and "an" are used to mean "at least one", "at least a first", "one or more" or "a plurality" of steps in the recited methods, except where specifically stated. This is particularly relevant to the administration steps in the treatment methods. Thus, not only may different doses be employed with the present invention, but different numbers of doses may be used.

3.0 DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

The present invention provides oral dentrifice compositions that comprise a therapeutically effective amount of at least a first steroidal hormone or steroidal hormone derviative, either alone or in combination with other therapeutic agents such as selective estrogen receptor modulators, progestins or progestogens, various steroid hormones such as testosterone and/or other agents effective in the treatment or prevention of osteoporosis. In

some instances, it may be desirable to provide a non-steroid substance in a form that is readily absorbed into the body, and which is conveniently administered in assoication with routine hygiene practice such as tooth brushing. Thus oral compounds designed to address erectile dysfunction, for example, may utilize formulations and administration methods disclosed herein.

The oral dentrifice compositions can also be combined with medications or enhancing agents to improve local absorption of estrogen. In particular embodiments of the invention, the estrogen used in such oral dentrifice compositions may be prepared using a variety of methods including, but not limited to, milling to micronize estrogen or incorporating estrogen into a caramelized base for dissolution of and absorption through the buccal and gingival mucosa into the systemic circulation.

The oral dentrifice compositions can be formulated, for example, as a toothpaste, tooth powder, mouth and gum powder, dental cream, ointment, prophylaxis paste, mouthwash, mouthrinse, lipid or non-lipid oral gel, lozenge, chewing gum, dental tablet, foaming dental tablet, pastille or an oral delivery device, such as a sublingual pellet, capsule, troche with organic mouth gel or a mouthguard or mouthpiece, impregnated with the at least a first estrogen or estrogen-containing substance.

In the early 1970s, estrogen was believed to be primarily a reproductive hormone, with effects limited to the uterus and mammary glands. Current concepts of estrogen action, however, are quite complex. Estrogen regulates the transcription of a limited number of genes. Unbound estrogens pass through cell membranes, spread within the cell and transport into the nucleus, where they bind and activate nuclear estrogen-receptor proteins found in tissues of the female reproductive system, breast, hypothalamus, pituitary, liver and bone of women. The activated estrogen-receptor complex then binds to specific acceptor proteins that recognize specific enhancer sites along the DNA sequence, enhancing transcription and stimulating the translation of those genes and as a result specific RNA and protein synthesis takes place. Estrogen appears to exert effects in tissues such as the bone, brain, eyes, teeth, vasomotor system, heart, breast, colon, and urogenital tract (Colditz *et al.*, 1995; Birge and Mortel, 1997; Paganini-Hill, 1995; Grodstein *et al.*, 1996a; Grodstein *et al.*, 1996b; Notelovitz, 1997).

Estrogen is required for converting vitamin D to calcitonin, which is essential for calcium absorption by the intestines. The use of estrogen and estrogen-containing substances increases serum levels of calcitonin, which in turn decreases bone resorption, maintains bone density and reduces risk of fracture. In addition maintaining skeletal integrity, estrogen has

been shown to be involved in reducing the incidence of atherosclerosis, and improving cardiovascular function. It may also be involved in enhancing cognition, preventing colon cancer, and protecting against macular degeneration.

The realization that estrogen affects so many functionally distinct tissues has prompted a reexamination of the models of estrogen receptor (ER) action, which were based on information accumulated from studies of the reproductive actions of the hormone. Until recently, the biological activity of estrogen was thought to be mediated by a single high-affinity estrogen receptor (ERα) located within a target cell nucleus. Thus, it was postulated that the primary determinant of whether a cell would respond to estrogen was the presence or absence of this receptor (O'Malley and Schrader, 1997; Clark and Peck, 1997). In this model, the role of estrogen was to bind to the receptor, switching it from an inactive to active state. More recently, however, research in this area has suggested that ER action is far more complex. It has now been established that there are at least two estrogen receptors, that ligands differentially alter the biochemical properties of the receptor, and that the resulting ligand/receptor complex is not recognized in the same fashion by all cells. Cumulatively, these findings help to explain how different estrogen receptor ligands manifest different biology in different cells.

The identification of a second estrogen receptor (ERβ) is one of the most important discoveries in estrogen action in the past 20 years (McDonnell *et al.*, 1995). The two receptors (ERα and ERβ) have a similar amino acid homology, with nearly identical DNA binding domains, suggesting these proteins activate the same genes. However, there is only approximately 60% similarity between the ligand binding domains of the receptors. Therefore, although the high affinity ligand estradiol interacts with both receptors in an equivalent manner, other compounds with preferential affinity for one receptor might exist, resulting in a different activity on each receptor. The discovery of more than one estrogen receptor may explain the tissue-selective actions of different estrogen receptor ligands. Studies of the hypothalamic area of the rat brain have identified cells that exclusively express ERα or ERβ as well as cells that co-express both receptors (Shugrue *et al.*, 1996, 1997). ERα is the dominant receptor in the arcuate and ventromedical nuclei, and ERβ is the dominant receptor expressed in the paraventricular and supraoptic nuclei. Both receptors are well expressed in the preoptic area and stria terminalis.

The identification of a second estrogen receptor and its differential expression in cells is an important component of tissue selectively. However, it has been observed that the

pharmacology of estrogens can differ between cells that express the same type of receptor. This has now been attributed to the fact that different estrogens have different effects on the structure of the estrogen receptor and that cells can distinguish between these shapes (McDonnell *et al.*, 1995). Thus, a new model of ER action has emerged. It is now considered that the ligand, agonist or antagonist, enters the cell and binds with a receptor, permitting its dimerization, leading to the formation of an ER/ligand complex with a unique molecular shape. The dimer in turn binds to a protein, or adaptor, that allows contact with the target gene control region. Interestingly, some adaptor proteins have very strict requirements as to the shape of the receptor complex with which they can interact. Other adaptor proteins are more promiscuous and can recognize several different types of ER/ligand complexes. Currently, at least 15 different adaptors have been identified. Thus, in addition to different receptors and different ligands, there are different adaptors whose expression level varies from tissue to tissue.

Selective estrogen receptor modulator (SERMs) have been described that have actions restricted to specific cell types. Tamoxifen and raloxifene are representative of the mixed agonists. For example, tamoxifen functions as a pure antagonist in estrogen receptor-positive breast cancer cells, is a partial agonist in the uterus, and appears to function as an agonist in bone (Love *et al.*, 1991, 1992). Raloxifen, another SERM, acts similarly to tamoxifen in bone, breast, and on lipoproteins, but appears to exhibit minimal agonist activity in the uterus (Draper *et al.*, 1993; Yang *et al.*, 1996).

The loss of estrogen associated with menopause is accompanied by many short- and long-term physical changes. These changes can be divided into early symptoms, intermediate physical changes and, later in life, diseases caused by long-term loss.

Early changes associated with estrogen loss are vasomotor instability (hot flashes) and night sweats. At menopause, approximately 85% of women experience hot flashes; it is for this change that women most commonly seek the advice of their physicians (Oldenhave *et al.*, 1993; Judd and Meldrum, 1981). Estrogen loss can also result in psychological effects, such as sleep disturbances, irritability, and mood disturbances, including depression. Physical changes such as vaginal atrophy, stress (urinary) incontinence, urinary tract infections, and onset of skin collagen loss signal intermediate changes associated with the decline in estrogen and can significantly affect a woman's quality of life.

The most significant concerns of estrogen loss, however, are those associated with long-term loss: cardiovascular disease, osteoporosis, Alzheimer's-type dementia, colon cancer,

and age-related macular degeneration. A woman who is experiencing early symptoms of menopause or who may have existing conditions or be at increased risk for these diseases should be counseled regarding estrogen replacement therapy (ERT) specifically and hormone replacement therapy, estrogen with progestogen (HRT), in general. Asymptomatic, healthy women with no known risk factors for late-stage diseases should also be counseled regarding ERT/HRT.

Women live approximately one-third of their lives in menopause. Osteoporosis is often associated with the onset of menopause. Postmenopausal osteoporosis affects the skeletal bones, including the jawbone. Jawbone density decreases with age resulting in bone loss that may result in the loss of teeth. Use of histochemical staining and immunoblotting has demonstrated the presence of estrogenic receptors in human pulp and the pulpo-dentinal border of human wisdom teeth (Hietala *et al.*, 1998). Studies have shown that estrogen prevents generalized osteoporosis, and there are reports that suggest that women on Estrogen Replacement Therapy (ERT) are less likely to be edentulous (Studd *et al.*, 1996; Ng *et al.*, 1993; Birkenfeld *et al.*, 1999). While these studies show the general utility of estrogen replacement therapy, there have been no reports of an oral dentrifice preparation affecting osteoporosis in the jawbone and preventing loss of teeth.

3.1 HORMONE REPLACEMENT THERAPY

In addition to prevention of osteoporosis, hormone replacement therapy is considered to relieve vasomotor symptoms, genital urinary tract atrophy, and mood and cognitive disturbances, as well as to prevent cardiovascular disease. It also may be considered to help prevent colon cancer, Alzheimer's disease, and adult tooth loss. Before therapy is instituted, a thorough medical evaluation is appropriate. The medical history should focus on contraindications to estrogen and precautions against risk factors and side effects, as discussed in detail below.

In women who elect to begin hormone replacement therapy, annual physical examinations, including breast and pelvic examinations, are recommended. Examinations include routine assessments such as blood pressure evaluation, Pap tests, lipid profile assessment, and mammography. In those women with a uterus, a progestin is generally prescribed, either in a sequential fashion (5-10 mg of medroxyprogesterone acetate for 12-14 days each month) or continuously (2.5 mg of medroxyprogesterone acetate per day). A

baseline endometrial biopsy is usually not necessary unless there is irregular bleeding; however, a biopsy is often performed for women with unexpected or excessive bleeding.

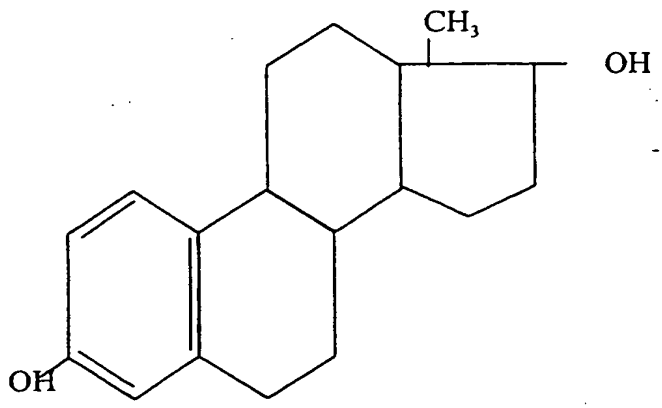
3.2 ESTROGEN AND ESTROGEN-CONTAINING SUBSTANCES

The metabolism of estrogen occurs mainly in the liver. Circulating estrogens, estradiol and estriol, are maintained in a dynamic equilibrium of metabolic interconversions. Estradiol converts reversibly to estrone. Both estradiol and estrone are converted to estriol. These three estrogens are conjugated by the liver and intestinal muscosa into different forms of estrogen sulfates and glucuronides, such as estrone-sulfate, estradiol-17-glucuronide and estriol-16-glucuronide.

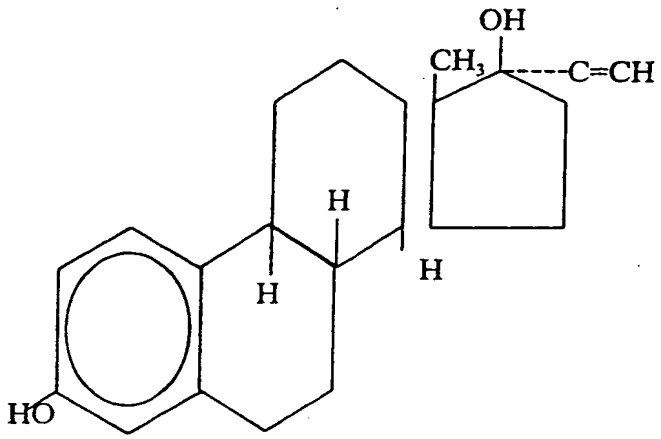
Before menopause in an adult female having normal menstrual cycles, the ovarian follicle secretes the major source of estrogen. Depending on the phase of the menstrual cycle, the follicle secrets about 70-500 μg of estradiol daily. It is known that estradiol is the primary intracellular human estrogen and is most 'potent' or provides the most stability of the activated estrogen-receptor complex when compared to estrone and estriol.

After menopause, the adrenal cortex secretes androsterodione, which is converted to estrone by peripheral tissues. Thus, estrone, the less active estrogen, is the most abundant form circulating in postmenopausal women.

Estradiol is a white, odorless, crystalline powder that is almost insoluble in water, freely soluble in alcohol, soluble in acetone, ether and chloroform and sparingly soluble in vegetable oils. Estradiol is chemically described as estra-1,3,5(10)-triene-3, 17β-diol, having an empirical formula and molecular weight of $C_{18}H_{24}0_2$ and 272.37, respectively. The structural formula of estradiol is:



Ethinyl estradiol is a white, odorless, crystalline powder steroidal synthetic derivative of natural estrogen, estradiol. It is insoluble in water, soluble in alcohol, chloroform, ether and vegetable oils. Ethinyl estradiol is chemically described as 19-Nor-17α-pregna-1,3,5(10)-trien-20-yne-3,17-diol, having an empirical formula and molecular weight of $C_{20}H_{24}0_2$ and 296.41, respectively. The structural formula of ethinyl estradiol is:



Although many estrogen preparations are available, in general the lowest effective estrogen dose that relieves the patient's symptoms and provides bone protection is used. The range for blood levels of estradiol that is considered necessary to maintain bone is generally considered to be between 40-50 pg/mL, with acceptable levels between 40-120 pg/mL and with optimal levels between 60-80 pg/mL (Speroff *et al.*, 1994; Taylor, 2000). Several of the more commonly used estrogen preparations for the prevention of osteoporosis and their conventional doses include: oral conjugated estrogen, 2.5 mg, 1.25 mg, 0.9 mg, 0.625 mg and 0.3 mg; oral micronized estradiol, 5 mg, 2 mg, 1.5 mg, 1 mg and 0.5 mg; oral synthetic steroidal ethinyl estradiol, 0.5 mg, 0.05 mg and 0.02 mg; oral synthetic conjugated estrogen, 0.625 mg and 0.9 mg; oral piperazine estrone sulfate, 0.75 mg estropipate and oral esterified estrogen, 0.3 mg (Lobo *et al.*, 1984; Physicians' Desk Reference®, 2000).

Dietary sources of estrogen such as phytoestrogens are available from soy, but due to their being weak estrogen agonists, very high doses, must be taken to achieve the therapeutic effects derived from hormone replacement therapy. For example, this study used a daily dietary supplementation of 60 g of isolated soy protein (Albertazzi *et al.*, 1998).

Oral estrogen preparations are initially transported to the liver *via* portal circulation, wherein liver conversion and hepatic degradation cause rapid clearance of the endogenous

hormone and alter the expected ratio of estradiol to estrone, thus making it less effective when administered orally. The addition of 17α-ethinyl to estradiol increases the potency and improves oral activity by impeding hepatic degradation.

In contrast, the oral dentrifice compositions of the present invention are not subject to the hepatic "first pass" effect, and circulating estrogen levels will mimic a steady state. Because the impact on liver metabolism is greater with oral than with transdermal administration of estrogen, at equivalent doses, oral therapy results in greater increases in HDL cholesterol, decreases in LDL cholesterol, and increases in triglycerides. Measurement of circulating estradiol levels may be useful as an estimate of estrogen effects on symptoms for those taking transdermal or vaginal estradiol preparations. For those taking oral preparations, particularly conjugated estrogens, measurement of estradiol serum levels does not accurately reflect estrogen activity. Follicle-stimulating hormone (FSH) levels remain in the postmenopausal range (<40 mIU/mL) for women taking hormone replacement therapy.

3.3 SELECTIVE ESTROGEN RECEPTOR MODULATORS (SERM)

The use of antiestrogens, such as tamoxifen as adjuvant chemotherapy for breast cancer in menopausal women and as prophylactic treatment for women at high risk for breast cancer, is associated with improved lipid profiles and increased bone density (Love *et al.*, 1992). These unexpected beneficial effects suggest that certain estrogen analogs such as tamoxifen may function as weak estrogen agonists in specific tissues such as bone, liver, and endometrium. These differences in estrogen activity may be explained in part by the recent discovery of a second type of estrogen receptor, the estrogen beta receptor. Clinical trials are being conducted with other estrogen analogs (now called selective estrogen receptor modulators or SERMs) such as raloxifene to assess their use as an alternative to traditional estrogen replacement therapy (Vignot and Meunier, 1999; de Valk-de Roo *et al.*, 1999).

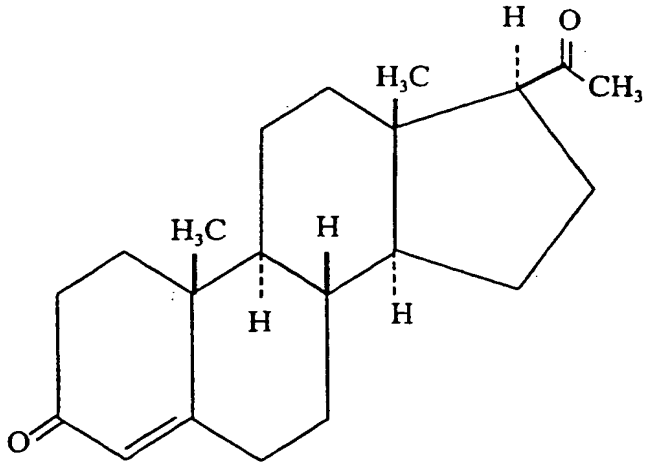
Raloxifene has been approved by the Food and Drug Administration for the prevention of postmenopausal osteoporosis. A daily dose of 60 mg of raloxifene is currently recommended for osteoporosis prevention. In a prospective randomized multicenter trial of over 600 menopausal women, raloxifene was shown to effectively protect against bone loss and reduce LDL cholesterol levels without inducing endometrial proliferation (Delmas *et al.*, 1997). In contrast to oral estrogens, levels of HDL cholesterol and triglycerides were unchanged during treatment. The risk of venous thromboembolic phenomena associated with raloxifene use appears to be similar to that of estrogen. In this study, there were no significant

differences in the proportions of women reporting hot flashes between the group receiving 60 mg of raloxifene daily and those taking placebo (26.3% and 22.7%). Thus, raloxifene would probably not be used in early menopausal women who are more likely to have hot flashes and other hypoestrogenic symptomatology.

3.4 PROGESTINS/PROGESTOGENS

There are several types of progestins that can be used in hormone replacement therapy, including medroxyprogesterone acetate, northindrone, micronized progesterone and megastrol acetate. The most commonly used progestin, medroxyprogesterone acetate, is a 21-carbon derivative of progesterone. A dose of 5-10 mg of medroxyprogesterone acetate during the last 12-14 days of estrogen administration is recommended to reduce the incidence of hyperplasia and endometrial cancer. Lower doses (2.5-5.0 mg) provide similar protection when given continuously with estrogen.

Progesterone is a white, odorless, crystalline powder synthesized from a starting material found in plants which is chemically identical to natural progesterone. It is practically insoluble in water, soluble in alcohol, acetone and dioxane and sparingly soluble in vegetable oils. Progesterone is chemically described as pregn-4-ene-3,20-dione, having an empirical formula and molecular weight of $C_{21}H_{30}0_2$ and 314.47, respectively. The structural formula of progesterone is:



Micronized progesterone preparations are available from individual pharmacies. Oral micronized progesterone in the dose range of about 100 to about 300 mg per day for 12 days per month (given in divided doses) is sufficient to protect against endometrial hyperplasia

(Gillet *et al.*, 1994; Hargrove *et al.*, 1989; Lane *et al.*, 1983). Progesterone is also used to treat infertile women and/or women having progestogen deficiency. Norethindrone, a 19-carbon compound, is the most potent oral progestin compound available for hormone replacement therapy. Doses of 1 mg are sufficient to induce endometrial secretory changes. Higher doses of norethindrone have been associated with elevations in LDL cholesterol.

3.5 COMBINATION TREATMENTS

In certain embodiments of the present invention, the at least a first estrogen, estrogen derivative or estrogen-containing substances are administered in combination with other steroidal hormones, biological and/or therapeutic agents, including, but not limited to, testosterone and derivatives thereof, progestins and derivatives thereof, selective estrogen receptor modulators, or other compounds useful in the treatment or prevention of osteoporosis.

Such hormonal combinations include, but are not limited to, estriol and estradiol, estradiol and micronized progesterone or natural progesterone, estradiol and testosterone, estriol, estradiol and micronized progesterone or natural progesterone, estriol, estradiol and testosterone, conjugated estrogen and micronized progesterone or natural progesterone, and conjugated estrogen and testosterone. Examples of such combinations include but are not limited to, conjugated equine estrogen combined with medroxyprogesterone acetate (avalible dose: 0.625 mg combined with 5.0 mg, respectively), esterified estrogen combined with methyltestosterone (avalible dose: 1.25 mg plus 2.5 mg, respectively) and micronized estradiol combined with micronized progesterone (avalible dose: 1 or 2 mg combined with 100 or 200 mg, respectively). Such homonal combinations may also be combined with other biological and/or therapeutic agents, including, but not limited to, progestins, selective estrogen receptor modulators, or other compounds useful in the treatment or prevention of osteoporosis. Examples of progestin compounds include, but are not limited to, medroxyprogesterone acetate (available doses include: 2.5, 5 and 10 mg), megestrol acetate (available doses include: 20 and 40 mg), norethindrone (norethisterone) (available doses include: 0.35 and 5 mg), micronized progesterone (available doses include: 100 and 200 mg), norethindrone acatate (available dose: 5 mg) and norgestron (available dose: 0.075 mg). Examples of antiosteoporosis agents include, but are not limited to, selective estrogen receptor modulators, such as tamoxifen or raloxifene (suggested dose: 60 mg), alendronate, calcitonin, calcium, fluoride, risedronate, etridronate, pamidronate, ipriflavone, germanium, vitamin K and vitamin D.

3.5.1 ESTROGEN/PROGESTOGEN

For perimenopausal women (around ages 45-50) who use low-dose oral contraceptives, it is difficult to determine whether menopause has actually occurred. Two practical approaches can be considered. In women 50 years of age or older, evaluating follicle stimulating hormone (FSH) levels at the end of the placebo week will provide an assessment of residual ovarian function. Women with FSH levels >40 mIU/ml can be started on hormone replacement therapy. Alternatively, switching from oral contraceptives to hormone replacement therapy can be tried empirically between the ages of 50 and 51 years. Because hormone replacement therapy does not effectively suppress ovarian function, those women with ovarian activity experience episodes of intermenstrual bleeding and increased breast tenderness.

In women who have an intact uterus, the addition of a progestin to the estrogen is necessary to prevent or reduce the risk of endometrial hyperplasia or endometrial cancer. In general, administration of progestins in sequential regimen is associated with cyclic, uterine withdrawal bleeding in a fairly predictable pattern. More recently, continuous administration of progestins has been studied in large multicenter trials. This approach results in a thin, atrophic endometrium, which can be associated with amenorrhea in up to 75% of individuals after 1 year. However, this amenorrheal response is not uniform, and many women will experience unpredictable vaginal spotting.

3.5.2 ESTROGEN-ANDROGEN REGIMENS

Two estrogen-androgen dose preparations that contain 5 mg, 2.5 mg and 1.25 mg of methyltestosterone, respectively, are available. Uptake of methyltestosterone is excellent, allowing supraphysiologic levels of testosterone to be achieved. The use of androgens has been shown to increase total cholesterol (increase LDL cholesterol and decrease HDL cholesterol). Other side effects can include hirsutism, acne, and weight gain.

3.5.3 ADDITIONAL ANTIOSTEOPOROSIS COMPOUNDS

Other compounds that have been reported to be effective in preventing bone loss include alendronate, calcium, sodium fluoride (Kleerekoper and Mendlovic, 1993), risedronate (Mortensen *et al.*, 1998), etridronate (Hanley *et al.*, 2000); pamidronate (Bravenboer *et al.*, 1999), ipriflavone (Moscarini *et al.*, 1994), germanium (Goodman, 1988), vitamin K (Iwamoto *et al.*, 1999; Yonemura *et al.*, 2000), vitamin D and intranasal use of calcitonin (Reginster *et al.*, 1995).

Calcium in known tc sustain development and maintenance of the bones and teeth. Vitamin D aids in the absorption of calcium from the intestines and the breakdown and assimilation of phosphorus, which is required for bone formation. Vitamin D also aids in the synthesis of enzymes found in mucous memebranes, which are involved in active transport of calcium. Without vitamin D, bones and teelth do not calcify properly.

Other nutrients that may be beneficial in treating and preventing osteoporosis include, but are not limited to, vitamin B_{12}, vitamin C, vitamin E, copper, magnesium and phosphorus.

A primary function of vitamin C is to maintain collagen, which is the protein necessary for formation of connective tissues of skin, ligaments and bones. Vitamin C promotes fine bone and tooth formation, and also protects the dentine and pulp. As reported by Rodale, a study of vitamin C deficient guinea pigs was performed wherein the dentine near developing teeth stopped forming and the pulp seperated from the dentine by liquid. Either dentine stopped forming, or the formation was not considered normal. The study observed shrinkage of the pulp and once seperated from the dentine, the pulp was found floating in the liquid. After administering vitamin C to the guinea pig, the study observed rapid repair of the dentine and pulp (1970).

It is known that serum levels of vitamin C are lowered by smoking. Nicotine added to a sample of human serum of known vitamin C concentration decreased the level of vitamin C in the serum by about 24 to 31% (Rodale, 1970).

Vitamin E may be involved in calcium metabolism. It is known that vitamin E prevents oxidation of the pituitary and adrenal hormones. Vitamin E also reduces the formation of thrombin that in turn reduces the probability of forming blood clots. The use of estrogen may neutralize the effect of vitamin E, causing collection of fibrin, which promotes blood clotting. As the collection of fibrin continues, the risk of thromboembolism inceases.

In addition to ERT/HRT, several bisphosphonates are currently approved for the treatment of osteoporosis or are undergoing investigation. The bisphosphonates inhibit resorption and produce an average 6% increase in spinal bone mineral density (Ott, 1993; Pacific *et al.*, 1988; Chestnut *et al.*, 1995; Rossini *et al.*, 1994). In a prevention trial that compared placebo, 5 mg alendronate, and estrogen (CEE 0.625 mg/day and progestin [MPA] 5mg/day), women treated with alendronate had a mean increase of 3.5% at the spine and 1.9% at the hip (Hosking *et al.*, 1998). Responses to HRT were 1 to 2 percentage points greater than alendronate. Those who received placebo lost bone mineral density. In a study of

approximately 2,000 women randomized to either placebo or alendronate, it was found that significantly fewer women in the alendronate group had vertebra fractures (Black *et al.*, 1996).

3.6 RISKS/BENEFIT ASSESSMENT OF HORMONE REPLACEMENT THERAPY

3.6.1 THROMBOEMBOLIC DISEASE

Recent studies have shown a twofold to fourfold increase in the risk of venous thromboembolism in users of estrogen-only and combined estrogen-progestin hormone replacement therapy (Daly *et al.*, 1996; Grodstein *et al.*, 1996c; Jick *et al.*, 1996). Because the absolute risk of venous thromboembolism in both users and nonusers of estrogen is low, there is only a modest increase in the morbidity associated with hormone replacement therapy, and this increased risk must be weighed against documented benefits. At the least, however, the risk factors for venous thromboembolism-such as family history of venous thrombosis, gross obesity, an earlier episode of thromboembolism and intercurrent illness associated with immobilization-should be considered in weighting the benefits and risks of hormone replacement therapy for any individual.

3.6.2 ENDOMETRIAL HYPERPLASIA AND ENDOMETRIAL CANCER

Long-term use of estrogen alone has been associated with the development of endometrial hyperplasia and endometrial cancer. The PEPI trial was the first large, prospective randomized study to examine the effects of unopposed estrogen over a 3-year follow-up period (PEPI Study Clinicians, 1996b). During the trial, women who took conjugated estrogen (0.625 mg) only were more likely to develop simple cystic hyperplasia (27.7%), adenomatous hyperplasia (22.7%), or atypical adenomatous hyperplasia (11.8%) than the placebo group (<0.8%). Women who took conjugated estrogen (0.625 mg) in combination with either cyclic (10 mg of medroxyprogestrone acetate per day for 12 days or 200 mg of micronized oral progesterone per day for 12 days) (*i.e.*, 200 mg given as a single dose once daily for 12 days) or continuous progestin therapy (2.5 mg of medroxyprogesterone acetate per day) had the same rate of hyperplasia as the placebo group. In those developing adenomatous or atypical adenomatous hyperplasia, the endometrium reverted to normal in 94% of women after treatment with progestin therapy (10 mg of medroxyprogesterone acetate per day for 3 months). Thus, in women with a uterus, cyclic or continuous progestin therapy is required to

protect the endometrium from hyperplastic transformation during estrogen replacement therapy (PEPI Study Clinicians, 1996b).

For women with previously diagnosed endometrial cancer, hormone replacement therapy remains an option that should be viewed cautiously. In a survey of members of the Society of Gynecologic Oncologists, 83% of respondents approved the use of estrogen replacement therapy in patients with state I, grade I, endometrial cancer; 56% favored using estrogen in cases of stage I, grade 2 cancer, and 39% would use estrogen in cases of stage I, grade 3 cancer. In women with a history of endometrial carcinoma, estrogens can be used for the same indications as for other women, except the selection of appropriate candidates should be based on prognostic indicators and the risk the patient is willing to assume. If the patient is free of tumor, the use of estrogen replacement therapy cannot result in recurrence. If an estrogen-dependent neoplasm is harbored somewhere in her body, it will eventually recur; however, the use of estrogen replacement therapy may result in an earlier recurrence (American College of Obstetricians and Gynecologists, 1996).

3.6.3 ENDOMETRIOSIS

For women with a history of endometriosis, treatment with estrogen-only regimens is not contraindicated. However, because these women often are younger than most menopausal women and may have undergone bilateral oophorectomy, higher doses of estrogen may induce the recurrence of endometriosis (Barbieri, 1992). If this occurs, discontinuing the estrogen therapy and beginning a progestin-only regimen can be an option.

3.6.4 BREAST CANCER

An increased risk of breast cancer has been associated with the extended duration of endogenous estrogen exposure such as that which occurs with early menarche, late menopause, and obesity. Although some studies have suggested that hormone replacement therapy is linked to an increased risk of breast cancer in postmenopausal women (Colditz *et al.*, 1995; Steinberg *et al.*, 1991), other studies have shown little or no relationship between estrogen use and breast cancer (Dupont and Page, 1991; Henrich, 1992). Despite the more than 50 epidemiologic studies published on this topic, no consistent link between hormone replacement therapy and breast cancer has been found. One possible interpretation of the data is that either there is no increased risk or the risk is too small to be shown clearly by epidemiologic studies. As for all women, those taking hormone replacement therapy should be encouraged to perform

monthly breast self-examinations have regular physical examinations, and have mammography every 1-2 years after age 40 and annually after age 50.

Because progestins potentially may stimulate the growth of breast tumors, the effects of the combination of estrogen and progestin on breast cancer risk also should also be considered. The results of studies that have examined this issue have been inconsistent (Bergkvist *et al.*, 1989). Various studies have shown estrogen-progestin therapy to increase, have no effect, or actually protect against breast cancer.

There are concerns that in women with previously diagnosed breast cancer, estrogen use may stimulate residual cancer cells to proliferate. However, there are no studies that support the concept that estrogen use leads to an increased risk of breast cancer recurrence or a change in the survival rate of these patients. Because women with prior breast cancer have an increased risk for a second primary breast cancer (Fornander *et al.*, 1989), close surveillance is warranted. Despite the well-recognized short-term and potential long-term benefits of hormone replacement therapy, it should be considered cautiously in women who have had breast cancer.

3.6.5 HYPERTENSION AND WEIGHT GAIN

In a large, randomized, prospective trial of women taking hormone replacement therapy, there were no significant differences in the mean systolic or diastolic brood pressures during the 3-year period of monitoring (PEPI Study Clinicians, 1995). Mean waist-to-hip ratios increased slightly over time for both the placebo and estrogen-treated groups. During the 3-year trial, the greatest weight gain (2.1 kg) occurred in the placebo group while the unopposed estrogen group had the lowest weight gain (0.7 kg).

4.0 DENTRIFICE FORMULATIONS AND PREPARATION

In addition to the at least a first steroidal hormone or steroidal hormone derivative, and other biological or therapeutic components, certain embodiments of the dentrifice formulations of the present invention comprise at least one or more of the following components: an abrasive or polishing agent, a fluoride ion source, a binder, a humectant, a surfactant or emulsifying agent, a thickening or consistency regulating agent, a chelating agent, a gelling agent, a sudsing agent, a pellicle film penetrating agent, a flavoring agent, a sweetening agent, an anticalculus agent, an antiplaque agent, an antigingivitis agent, a pigment or coloring agent,

an antibacterial agent, a whitening agent, a preservative, a stannous salt or water. The foregoing components are described in more detail below.

Another preferred embodiment of the present invention is a mouthwash composition. Conventional mouthwash composition components can comprise the carrier for the active agents of the present invention. Mouthwashes generally comprise from about 20:1 to about 2:1 of a water/ethyl alcohol solution and preferably other ingredients such as flavor, sweeteners, humectants and sudsing agents such as those described herein. The humectants, such as glycerin and sorbitol give a moist feel to the mouth. Generally, a mouthwash or mouthrinse according to this invention may contain, for instance, up to about 20% of ethyl alcohol, about 0% to about 50% of humectant, about 0.1 to 5% of an emulsifying agent (surfactant), about 0% to 0.5% of a sweetening agent, about 0.03% to 0.3% of a flavoring agent.

4.1 ABRASIVES AND POLISHING AGENTS

Precipitated silica abrasives, as disclosed in U. S. Patent Nos. 5,279,815 and 5,716,601, each incorporated herein by reference, are particularly suitable for incorporation into fluoride-containing therapeutic oral dentrifice compositions. Therapeutic toothpastes employing such abrasives provide satisfactory tooth cleaning performance and also possess excellent abrasive fluoride compatibility characteristics. In particular aspects of the invention, the compositions contain from about 6% to 35%, preferably from about 10% to 20%, by weight of the precipitated silica abrasives.

In other aspects of the present invention, the compositions contain calcium phosphate materials as abrasives. Such calcium materials are described in U. S. Patent Nos. 3,624,199, and 3,864,471, each incorporated herein by reference. In further aspects, the compositions contain alkaline earth metal ions, such as calcium ions, as described in U. S. Patent No. 3,991,177, incorporated herein by reference. Other suitable alkaline earth metal compounds or ions include those described in U. S. Patent Nos. 3,095,356, 3,122,483, 3,669,221, 3,782,446, 3,842,168 and, 3,689,537, each incorporated herein by reference. Other suitable abrasives include those described in U. S. Patent Nos. 5,449,509, 4,340,583, 3,937,321, 3,937,803, 3,937,804, 3,943,240, 4,160,022, 4,547,362, 4,623,536, 4,663,153, 4,721,614, 4,943,429 and 3,574,823, each incorporated herein by reference.

4.2 FLUORIDE ION SOURCE

In some embodiments, the instant oral dentrifice compositions contain from about 0.005% to 3%, preferably from about 0.1% to 1.0%, by weight of a water-soluble, fluorine-containing material which yields fluoride ions in aqueous solutions. The sources of fluoride ions, or fluoride-providing component are well known in the art as anti-caries agents. These compounds may be slightly soluble in water or may be fully water-soluble. They are characterized by their ability to release fluoride ions in water and by substantial freedom from undesired reaction with other compounds of the oral preparation. Among these materials are inorganic fluoride salts, such as soluble alkali metal, alkaline earth metal salts, for example sodium fluoride, potassium fluoride, ammonium fluoride, calcium fluoride, a copper fluoride such as cuprous fluoride, zinc fluoride, barium fluoride, sodium fluorosilicate, ammonium fluorosilicate, sodium fluorozirconate, ammonium fluorozirconate, sodium monofluorphosphate, aluminum mono-and di-fluorophosphate, and fluorinated sodium calcium pyrophosphate. Alkali metal and tin fluorides, such as sodium and stannous fluorides, sodium monofluorophosphate (MFP) and mixtures thereof, are preferred. Such fluoride ions combine with dental enamel and thereby reduce enamel solubility in acid. Application of fluoride ions to dental enamel serves to protect teeth against decay.

A wide variety of fluoride ion-yielding materials can be employed as sources of soluble fluoride in the instant compositions. Examples of suitable fluoride ion-yielding materials are found in U.S. Patent Nos. 3,535,421 and 3,678,154, each incorporated herein by reference. Preferred fluoride ion sources for use herein include sodium fluoride (NaF), stannous fluoride (SnF_2), potassium fluoride (KF), potassium stannous fluoride (SnF_2-KF), indium fluoride (InF_3), zinc fluoride (ZnF_2), ammonium fluoride (NH_4F), and stannous chlorofluoride (SnC1F). Sodium fluoride and stannous fluoride are particularly preferred as well as mixtures thereof.

Preferably, the disclosed compositions provide from about 50 ppm to 500 ppm, more preferably from about 100 to 400 ppm, of fluoride ions in the aqueous solutions which contact dental surfaces when the oral dentrifice compositions of the present invention are used in the mouth. Such solutions can be formed by preparing 3:1 water/toothpaste slurries (by weight) of the compositions herein and by subsequently centrifuging such slurries to obtain an aqueous supernatant. The fluoride ion concentration in such a supernatant is taken as a measure of the "soluble fluoride" provided by any given fluoride dentrifice composition.

A composition of the invention may optionally contain other agents known to enhance the anticaries effect of fluoride and monofluorophosphate, for instance, calcium

glycerophosphate (which is known to enhance the anticaries activity of monofluorophosphate), which may be incorporated in a weight ratio of up to 1:3, preferably 1:20 to 1:3, compared to the total weight of monofluorophosphate.

4.3 BINDERS

In additional aspects of the invention, binders are employed to prevent separation of the liquid and solid phases in certain of the dentrifice compositions herein. Such binder materials are well known in the toothpaste art. The most conventionally used binders are the seaweed colloids such as Carrageenen (Irish moss or Viscarin®) and derivatives of cellulose, such as sodium carboxymethyl cellulose and hydroxyethyl cellulose. Other types of binders suitable for use herein are gums such as vegetable gums, *e.g.*, guar gums and fermentation products, *e.g.*, xanthan gum. The binder component generally comprises from about 0.1% to 5%, preferably 0.2% to 2% by weight of the compositions herein.

Toothpaste binders are more fully described in U.S. Patent Nos. 2,839,448 and 3,962,307, incorporated herein by reference.

4.4 HUMECTANTS

In further aspects of the invention, the compositions herein comprise a humectant. Suitable humectant materials are also well known in the toothpaste art. Humectants serve to retain moisture and keep the toothpaste compositions from hardening upon exposure to air. Certain humectants can also impart desirable sweetness or flavor to toothpaste compositions. The humectant generally comprises from about 5% to 70%, preferably from about 20% to 35%, by weight of the compositions herein.

Suitable humectants for use in this invention include edible polyhydric alcohols such as glycerin, sorbitol, xylitol and propylene glycol. Sorbitol is frequently employed as a 70% aqueous solution known as Sorbo Mixtures®. Mixtures of glycerin and sorbitol are especially preferred as the humectant component of the toothpaste compositions herein.

4.5 SURFACTANTS, SUDSING AND EMULSIFYING AGENTS

A preferred optional ingredient is a surfactant, emulsifying or sudsing agent. Suitable agents are those which are reasonably stable and form suds throughout a wide pH range, *i.e.*, non-soap anionic, nonionic, cationic, zwitterionic and amphoteric organic synthetic detergents.

Agents of these types are described more fully in U.S. Patent Nos. 4,889,712, 4,051,234, 3,959,458 and 3,937,807, each incorporated herein by reference.

Anionic sudsing agents useful herein include the water-soluble salts of alkyl sulfates having from 8 to 18 carbon atoms in the alkyl radical and the water-soluble salts of sulfonated monoglycerides of fatty acids having from 10 to 18 carbon atoms. Sodium lauryl sulfate and sodium coconut monoglyceride sulfonates are examples of anionic surfactants of this type. Mixtures of anionic surfactants can also be employed.

The nonionic sudsing agents which can be used in the compositions of the present invention can be broadly defined as compounds produced by the condensation of alkylene oxide groups (hydrophilic in nature) with an organic hydrophobic compound which may be aliphatic or alkyl-aromatic in nature. Examples of suitable nonionic sudsing agents include the Pluronics, polyethylene oxide condensates of alkyl phenols, products derived from the condensation of ethylene oxide with the reaction product of propylene oxide and ethylene diamine, ethylene oxide condensates of aliphatic alcohols, long chain tertiary amine oxides, long chain tertiary phosphine oxides, long chain dialkyl sulfoxides and mixtures of such materials.

The zwitterionic synthetic surfactant or sudsing agents useful in the present invention can be broadly described as derivatives of aliphatic quaternary ammonium phosphonium, and sulfonium compounds, in which the aliphatic radicals can be straight chain or branched, and wherein one of the aliphatic substituents contains from about 8 to 18 carbon atoms and one contains an anionic water-solubilizing group, *e.g.*, carboxy, sulfonate, sulfate, phosphate, or phosphonate, such as 4-(N,N-di(2-hydroxyethyl)-N-octadecylammonio)-butane-1-carboxylate.

The cationic agents useful in the present compositions can be broadly defined as quaternary ammonium compounds having one long alkyl chain containing from about 8 to 18 carbon atoms such as lauryl trimethylammonium chloride; cetyl pyridinium chloride; cetyl trimethylammonium bromide; di-isobutyl-phenoxyethoxyethyl-dimethyobenzylammonium chloride; coconutalkyltrimethylammonium nitrite; cetyl pyridinium fluoride, and such like. Especially preferred are the quaternary ammonium fluorides described in U.S. Patent No. 3,535,421, incorporated herein by reference, where said quaternary ammonium fluorides have detergent properties. The cationic agents can also act as germicides in certain of the compositions herein.

The amphoteric agents useful in the present invention can be broadly described as derivatives of aliphatic secondary and tertiary amines in which the aliphatic radical can be

straight chain or branched and wherein one of the aliphatic substituents contains from about 8 to 18 carbon atoms and one contains an anionic water-solubilizing group, *e.g.*, carboxylate, sulfonate, sulfate, phosphate or phosphonate, such as N-alkyltaurines (*e.g.*, reaction product of dodecylamine and sodium isethionate) and Miranol.

In compositions of the invention comprising these agents, the agents can be present in the in an amount from 0.1% to 6% by weight of the total composition.

4.6 THICKENING AND CONSISTENCY REGULATING AGENTS

In preparing certain of the instant toothpaste compositions, thickening material is added to provide a desirable consistency. Preferred thickening agents are carboxyvinyl polymers, carrageenan, hydroxethyl cellulose and water soluble salts of cellulose ethers such as sodium carboxymethyl cellulose and sodium carboxymethyl hydroxethyl cellulose. Natural gums such as gum karaya, xanthan gun, gum arabic, and gum tragacanth can also be used. Thickening agents in an amount from 0.5% to 5.0% by weight of the total composition can be used.

4.7 CHELATING AGENTS

Another preferred optional agent is a chelating agent selected from the group consisting of tartaric acid and pharmaceutically-acceptable salts thereof, citric acid and alkali metal citrates and mixtures thereof. Chelating agents are able to recognize complex calcium found in the cell walls of the bacteria. Chelating agents can also disrupt plaque by removing calcium from the calcium bridges that help hold this biomass intact. However, it is possible to use a chelating agent that has a high affinity for calcium that may result in tooth demineralization. This is contrary to the objects and intentions of the present invention and care must be taken in the selection of an appropriate chelating agent.

Sodium and potassium citrate are preferred alkali metal citrates, with citric acid/alkali metal citrate combinations also preferred in certain aspects. Preferred salts of tartaric acid include disodium tartrate, dipotassium tartrate, sodium potassium tartrate, sodium hydrogen tartrate and potassium hydrogen tartrate. The amounts of chelating agent suitable for use in the present invention are about 0.1% to about 2.5%, preferably from about 0.5% to about 2.5% and more preferably from about 1.0% to about 2.5% by weight of the composition. The tartaric acid salt chelating agent can be used alone or in combination with other optional chelating agents, such as soluble pyrophosphates and anionic polymeric polycarboxylates, such as those described in U. S. Patent Nos. 4,138,477 and 4,183,914, incorporated herein by reference.

4.8 GELLING AGENTS

It is also preferred to use, in those compositions of the invention that are formulated as toothpastes, a gelling agent such as a natural or synthetic gum or gum-like material. Whilst non-ionic gums such as guar gum or xanthan gum are particularly preferred, other gums or gum-like materials, such as, for example, Irish Moss, gum tragacanth, sodium carboxymethylcellulose, polyvinylpyrrolidone, starch or a thickening silica may also be used. The gelling agent content is usually from 0.001 to 10%, preferably 0.01 to 5% by weight of the composition.

4.9 FLAVORING AND SWEETENING AGENTS

Flavoring agents can also be added to the instant compositions. Suitable flavoring agents include oil of wintergreen, oil of peppermint, oil of spearmint, oil of sassafras and oil of clove. Sweetening agents which can be used include sucrose, lactose, maltose, sorbitol, xylitol, sodium cyclamate, perillartine, AMP (aspartyl phenyl alanine, methyl ester), saccharin, dextrose, levulose, aspartame, D-tryptophan, acetosulpham, dihydrochalcones, sodium cyclamate and the like. Flavoring agents are generally used in the instant compositions at levels of from about 0.01% to 2% by weight, and sweetening agents at levels of from about 0.05% to about 3% by weight.

4.10 ANTICALCULUS, ANTIPLAQUE AND ANTIGINGIVITIS AGENTS

Phosphorus-containing anticalculus (antitartar) agents and/or bis-biguanide antiplaque agents can also optionally be added to the compositions of this invention. Phosphorus-containing anticalculus agents such as disodium ethane-1-hydroxy-1, 1-diphosphonate and related materials are described more fully in U. S. Patent No. 3,488,419, incorporated herein by reference. Bis-Biguanide antiplaque agents such as chlorhexidine (1,6-bis[N^5-p-chlorophenyl-N^1-biguanido]hexane), the soluble and insoluble salts thereof and related materials such as 1,2-bis(N^5-p-trifluoromethylphenyl-N^1-biguanido) ethane are described more fully in U. S. Patent Nos. 3,934,002 and 3,937,807, and Belgian Patents 843,244, and 844,764, each incorporated herein by reference. Additional antiplaque compositions are those comprising a bacteriocin such as nisin and a polyphosphonate, as described in U. S. Patent No. 5,840,281, and the antiplaque agents described in U. S. Patent Nos. 3,696,191, 3,991,177, 4,058,595, 4,115,546, 4,138,476, 4,140,758, 4,154,815, 4,737,359, 4,986,981, 4,992,420, 5,000,939,

4,652,444, 4,725,428, 4,355,022, 5,292,500 and 5,681,548, each incorporated herein by reference.

Other suitable anticalculus agents are described in U. S. Patent Nos. 5,531,983, 5,318,773, 4,627,977, 4,515,772, 4,590,066, 4,684,518, 4,806,339, 4,885,155 and 4,999,184, 4,806,340, 4,931,273 4,627,977, 4,806,342, 4,869,898 4,806,340, 4,906,456, 4,925,654, 4,931,273 and 4,966,777, incorporated herein by reference. Suitable antigingivitis agents include those described in U. S. patent 5,683,678, incorporated herein by reference.

If present, the optional anticalculus and/or antiplaque agents generally comprise from about 0.01% to 2.5% by weight of the compositions herein.

4.11 PIGMENTS AND COLORING AGENTS

A variety of other optional components well known in the art may be added to the compositions herein to improve the usual aesthetics. These include pigments, dyes, speckles and the like. When present, these optional components generally comprise from about 0.001 to about 2% by weight of the oral dentrifice compositions.

4.12 ANTIBACTERIAL AND PRESERVATIVE AGENTS

Since the natural and synthetic water dispersions of water binders are subject to microbial or mold attack, the instant compositions herein may optionally contain a relatively small amount of a preservative. Examples of preservatives typically employed are the esters of parahydroxyl benzoates.

Other suitable oral antiseptic compositions are those comprising a combination of boric acid, benzoic acid, menthol, methyl salicylate, thymol and eucalyptol as described in U. S. Patent No. 3,164,524, incorporated herein by reference. Water-insoluble noncationic antibacterial agents such as triclosan, as described U. S. Patent Nos. 4,894,220, 4,002,880 and 4,749,562, incorporated herein by reference, are also suitable for use in the present invention.

4.13 WHITENING AGENTS

In certain aspects of the invention, the oral dentrifice compositions also comprise whitening agents, such as titanium dioxide.

4.14 STANNOUS SALTS

Also desirable for inclusion in certain embodiments of the compositions of the present invention are other stannous salts such as stannous pyrophosphate and stannous gluconate, and antimicrobials such as quaternary ammonium salts, such as cetyl pyridinium chloride and tetradecylethyl pyridinium chloride, bisbiquanide salts, copper bisglycinate, nonionic anti microbial salts and flavor oils. Such agents are disclosed in U.S. Patent Nos. 2,946,725 and 4,051,234, incorporated herein by reference. Other optional components include buffering agents, bicarbonates, peroxides, nitrate salts such as sodium and potassium nitrate. These agents, if present, are included at levels of from about 0.01% to about 30% by weight of the composition.

4.15 WATER

In certain aspects of the invention, water is an element of the oral dentrifice compositions. Water employed in the preparation of commercially-suitable compositions should be deionized and free of organic impurities. Water typically comprises less than 10% by weight.

4.16 TOOTHPASTE COMPOSITIONS

The components of the oral dentrifice compositions that are formulated as toothpastes and tooth gels generally include one or more of the following: a dental abrasive (from about 10% to about 50%); a surfactant (from about 0.5% to about 10%); a thickening agent (from about 0.1% to about 5%); a humectant (from about 10% to about 55%); a flavoring agent (from about 0.04% to about 2%); a sweetening agent (from about 0.1% to 55%); a coloring agent (from about 0.01% to about 0.5%); and water (from about 2% to about 45%). In certain aspects, the toothpastes also include one or more anticaries agents (from about 0.05% to about 0.3% as fluoride ion).

4.17 METHOD OF ADMINISTRATION

The estrogen compositions and other compositions described herein are administered in any form as described herein for application to the gum and sub-gum area, and absorbed through the trans-mucosal membrane into the systemic circulation. The toothpaste is applied to the oral labio-buccal mucosa and gingiva for at least about 2 to about 5 minutes. Most of the composition is expectorated following such contact, followed by rinsing the mouth with

water. The frequency of such contact is once or twice daily, three times a week or only in the evenings, by brushing teeth with the toothpaste.

5.0 ASSAYS

A primary assay used to determine the presence of osteoporosis, and in determining the efficacy of treatment regimens is bone densitometry, for example dual energy X-ray absorptiometry (DEXA). Information provided by measurements of bone mineral density can be augmented with the use of biochemical markers that predict bone loss, bone density, and the risk of fractures. Urinary markers of bone resorption can predict bone mineral density response to and therapeutic effect of ERT/HRT (Chestnut *et al.*, 1997; Garnero *et al.*, 1996b) much more quickly than bone densitometry. They are not, however, useful in predicting which patient has already developed osteoporosis.

Research into bone metabolism and into biochemical markers of the remodeling process has grown in intensity and complexity in the 1990s. Population-based studies using biochemical markers have demonstrated an association between high levels of bone turnover and accelerated bone loss (Calvo *et al.*, 1996). Currently, the best biochemical indices of bone formation (osteoblastic activity) are bone specific alkaline phosphatase (BSAP) and serum osteocalcin. Assays for procollagen type I propeptides also are in use.

Urinary markers of bone resorption have been used more broadly than indices of bone formation, however. This is due in large part to the fact that when monitoring the effects of antiresorptive agents such as exogenous estrogen and bisphosphonates, bone resorption markers provide an earlier indication of therapeutic effect on bone than do formation markers. Resorption markers include hydroxyproline, galactosyl hydroxylysine (GHYL), and pyridinoline cross-links (which can be measured in urine in total, free, or peptide-bound forms, such as N- and C-terminal telopeptides). Serum levels of tartrate-resistant acid phosphatase (TRAP) also have been employed. Of these, urinary breakdown products specific to type I collagen are proving to be the best markers. Type I collagen accounts for about 90 percent of the organic matrix of bone.

5.1 TYPE I COLLAGEN-BASED MARKERS

When measuring degradation products of collagen in urine, it is important to recognize that not only is bone being continuously catabolized in the body, many other connective tissues

that contain collagen are also subject to turnover. A marker that is specific to bone and/or the osteoclastic resorption process is therefore highly desirable. In fact, the ideal marker of bone resorption would be a specific product of osteoclastic activity that is not further metabolized before clearance by the kidneys and excretion in the urine. Such a marker would measure collective ostoclastic activity in the whole body and reflect recent (within a few hours) resorption activity.

The tensile strength of the collagen figure relies on chemical cross-links between the component collagen molecules. Pyridinolines are prominent cross-linking amino acids in collagen. The collagen molecule consists of three polypeptide threads twisted together leaving short sequences of amino acids at each end. These telopeptides at both ends are critically involved in cross-linking. They are termed N-telopeptides and C-telopeptides. Cross-linked N-telopeptides (NTx) and cross-linked C-telopeptides (CTx) have been isolated from urine. They represent short peptide fragments (~8 amino acid residues) still linked through the pyridinoline cross-links. The cross-link is presumed to protect these peptide sequences from degradation during osteoclastic resorption and passage through the body.

The cross-linked N-telopeptide, NTx, urinary analyte embodies an epitope recognized by an antibody that is the basis of the NTx immunoassay. The pryidinoline cross-link is not a part of this recognized epitope. The 8-amino acid sequence of the telopeptide is the essential measurement provided by the assay. This sequence originates in the β2(1) collagen chain and has to be cross-linked (*i.e.*, it originates from a degraded fibril rather than a newly made collage molecule) and is generated by cleavage at a particular peptide linkage in the parent collagen molecule. Thus, NTx measurements in urine provide a selective index of osteoclastic activity on bone collagen.

5.2 MEASURING NTx LEVELS

The NTx immunoassay referenced above is a urine test (Osteomark, Ostex International, Seattle) performed in the clinical laboratory. It provides a specific quantitative measurement of the excretion of cross-linked N-telopeptides (NTx). Since NT x is generated during osteoclastic activity, elevated levels of urinary NTx indicate elevated bone collagen breakdown and, thus, bone resorption (Apone *et al.*, 1994; Hanson *et al.*, 1992).

NTx values are corrected for urinary dilution by creatinine analysis and reported as nanomole of bone collagen equivalents per millimole of creatinine (nM BCE/mM creatinine). Results are compared to a standard female reference range of 5 to 65 (range derived from the

mean of 35 ± 2 SD), which is based on a reference population of healthy premenopausal women.

Other urine-based bone resorption markers include the Pyrilinks-D® fDpd assay (Metra Biosystems, Mountain View, Calif.) and the Cross Laps™ C-telopeptide assay (Osteometer Biotech A/S, Rodovre, Denmark).

Radioimmunoassy of estradiol will be assayed using an established radioimmunoassay that uses an established kit procedure (Diagnostic Systems Laboratories Inc., Webster, TX). Estrogen receptors, α and β forms, will be localized in the tissue using a radioreceptor assay that uses immunocyto-chemical procedures established in the laboratory. The peroxidase-anti-peroxidase procedure will be employed in paraffin embedded tissue. 3, 3′ diaminobenzadine will be used as the chromogens. Photographs of control and experimental tissues will be obtained.

6.0 THERAPEUTIC KITS

The present invention also provides therapeutic kits comprising the agents of the present invention described herein. Such kits will generally contain, in suitable container, a pharmaceutically acceptable formulation of an oral dentrifice composition comprising a therapeutically effective amount of at least a first steroidal hormone or steroidal hormone derivative, in accordance with the invention. The kits may also contain other pharmaceutically acceptable formulations, such as any one or more of a range of therapeutically beneficial compounds or drugs.

The kits may have at least a first suitable container that contains the oral dentrifice composition, with or without any additional components, or they may have distinct container for each desired agent. Certain preferred kits of the present invention include at least a first oral dentrifice composition, such as a toothpaste, that comprises a therapeutically effective amount of at least a first steroidal hormone or steroidal hormone derivative, packaged in a kit with a toothbrush or a mouthguard or mouthpiece. In such kits, the toothpaste can be pre-complexed with the toothbrush or the mouthguard or mouthpiece, or each of the components of the kit may be maintained separately within distinct containers prior to use.

The kits may further comprise at least a first progestin, progestogen, progesterone compound or a derivative thereof, a testosterone compound or derivative thereof, an antiosteoporosis agent or a combination of any one or more of these compounds or agents with the estrogen compound. Instructions for use may also be provided in any of these kits.

When the components of the kit are provided in one or more liquid solutions, the liquid solution is an aqueous solution, with a sterile aqueous solution being particularly preferred. However, the components of the kit may be provided as dried powder(s). When components are provided as a dry powder, the powder can be reconstituted by the addition of a suitable solvent, such as water, that may be provided in another container.

The kits of the present invention will also typically include a means for containing the components in close confinement for commercial sale, such as, *e.g.*, injection or blow-molded plastic containers into which the desired compositions and other apparatus are placed and retained.

The following examples are included to demonstrate preferred embodiments of the invention. It should be appreciated by those of skill in the art that the techniques disclosed in the examples which follow represent techniques discovered by the inventor to function well in the practice of the invention, and thus can be considered to constitute preferred modes for its practice. However, those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments which are disclosed and still obtain a like or similar result without departing from the spirit and scope of the invention.

7.0 EXAMPLES

7.1 EXAMPLE 1

ESTROGEN TOOTHPASTE FOR PREVENTION OF OSTEOPOROSIS OF ALVEOLAR BONE AND LOSS OF TEETH

A series of women were enrolled in a trial of an estrogen-containing toothpaste (in the form of estradiol). Postmenopausal women not on Estrogen Replacement Therapy (ERT) with no contraindication to the usage of estrogen qualified for this study. Contraindications to the use of estrogen include a history of or active thromboembolism, undiagnosed vaginal bleeding, known or suspected breast cancer, estrogen dependent neoplasia and pregnancy.

The patients were given a detailed dental evaluation, pretreatment serum estradiol levels determined, and Bone Mass Density (BMD) of the jaw bones, and femoral bone and spinal cord obtained by dual energy X-ray absorptiometry (DEXA). The patients were given the estrogen toothpaste, and required to brush their teeth twice per day, for up to 3 minutes each brushing. About 1-2 mg of estradiol is administered per aliquot of toothpaste. Patients who had not had a hysterectomy were given about 2.5 mg of Provera® (medroxyprogesterone acetate) per day, in order to reduce the risk of uterine cancer. Periodic blood tests were

performed to assess estrogen levels in blood, and Bone Mass Density measurements were compared to the base line values to evaluate the therapeutic benefit.

7.2 EXAMPLE 2

TOOTHPASTE COMPRISING ESTRADIOL AND PROGESTERONE

A series of women are enrolled in a trial of an oral dentrifice composition, in this case a toothpaste, which comprises therapeutically effective amounts of micronized powder estradiol and mirconized progesterone. Postmenopausal women having an intact uterus not on Estrogen Replacement Therapy (ERT) with no contraindication to the usage of estrogen qualify for this study. Contraindications to the use of estrogen include a history of or active thromboembolism, undiagnosed vaginal bleeding, known or suspected breast cancer, estrogen dependent neoplasia and pregnancy.

The participants have 3 cc of their blood drawn using a 22-gauge needle in a red-top test tube. Each test tube is spun in a centrifuge to separate the serum. The serum contained in each test tube is removed with a pipette and placed in another test tube labeled with the date, time and subject number, respectively.

Using a sensitive weighing scale graduated to 0.001 g, the toothpaste is weighed. Three readings are taken to assess amount of toothpaste squeezed on a regular toothbrush using a plastic graduated syringe having 20 cc capacity, each mark representing 1 cc. The amounts are noted and average amount in grams is obtained.

Wax paper is placed on the scale and the scale is zeroed. The entire amount of toothpaste within the container is squeezed onto the wax paper and the total weight of the toothpaste is obtained. Using a calculator, it is determined how much estradiol and pergesterone are required so that each application of toothpaste contains 1 mg of estradiol and 100 mg of progesterone.

The micronized powder estradiol and micronized progesterone are weighed using the scale again. The estradiol and progesterone are now added to the toothpaste and mixed thoroughly for about 15–20 minutes using a spatula. A plastic graduated syringe having a 20 cc capacity, each mark representing 1 cc, is filled with the estradiol/progesterone containing toothpaste. One application of toothpaste corresponds to 1 cc.

One application of the toothpaste is dispensed onto a toothbrush using the syringe. The participants then brush their teeth with the estradiaol/progesterone containing toothpaste and

are required to brush their teeth and gums once a day for two minutes during each brushing using a Sonicare®-timed (©Optiva Corporation; Bellevue, Washington) electric toothbrush.

Participants' blood is redrawn at about 1, 2, 6, 12 and 24 hours later, centrifuged and the serum saved in a test tube labeled with the date, time and subject number, respectively. These samples are then tested for serum estradiol and progesterone levels.

7.3 EXAMPLE 3

TOOTHPASTE COMPRISING ESTRADIOL AND SERUM ESTRADIOL LEVELS

A study of blood estradiol levels in postmenopausal women was performed. Four postmenopausal females not on ERT with no contraindication to the usage of estrogen were selected. Contraindications to the use of estrogen included a history of or active thromboembolism, undiagnosed vaginal bleeding, known or suspected breast cancer, estrogen dependent neoplasia and pregnancy. The participants had 3 cc of their blood drawn using a 22-gauge needle in a red-top test tube. Each test tube was spun in a centrifuge to separate the serum. The serum contained in each test tube was removed with a pipette and placed in another test tube labeled with the date, time and subject number (1-4), respectively.

Using a sensitive weighing scale graduated to 0.001 g, Colgate® Cavity Protection Winterfresh® Gel toothpaste (Colgate-Palmolive Company, New York, NY) was weighed. Three readings were taken to assess amount of toothpaste squeezed on a regular toothbrush using a plastic graduated syringe having 20 cc capacity, each mark representing 1 cc. The amounts were noted and average amount in grams was obtained.

Wax paper was placed on the scale and the scale was zeroed. The entire amount of toothpaste within the container was squeezed onto the wax paper and the total weight of the toothpaste was obtained; 150 g toothpaste. Using a calculator, it was determined that 111 mg of estradiol was required so that each application of toothpaste contained 1 mg of estradiol.

Micronized powder estradiol was obtained from Spectrum Chemical MFG Corp. and weighed using the scale again. 111 mg of the estradiol was added to the 150 g toothpaste and mixed thoroughly for about 15–20 minutes using a spatula. No alteration in the taste, texture, or color of the toothpaste was observed. A plastic graduated syringe having a 20 cc capacity, each mark representing 1 cc, was filled with the estradiol containing toothpaste. One application of toothpaste corresponded to 1 cc. Alternatively, one unit dose is 1cc of toothpaste, which contains 1 mg of of estradiol.

One application of the toothpaste was dispensed onto a toothbrush using the syringe. The participants then brushed their teeth with the estradiaol containing toothpaste and were required to brush their teeth and gums once a day for two minutes during each brushing using a Sonicare®-timed (©Optiva Corporation; Bellevue, Washington) electric toothbrush.

Participants' blood was redrawn at about 1, 2, 6, 12 and 24 hours later, centrifuged and the serum saved in a test tube labeled with the date, time and subject number (1-4), respectively. These samples were then tested for serum estradiol levels (See Table 1).

Table 1

Serum Estradiol Levels after Brushing Teeth with Estradiol Containing Toothpaste

	Control	1 hour	2 hour	6 hour	12 hour	24 hour
Subject 1	8.2	165	109	33	387	90
Subject 2	11.2	753	284	700 (8 hr)	204	225
Subject 3	66	1146	486	252	--	153
Subject 4	20	249	62	31	--	22

Units: picogram of estradiol/mL of serum.

As shown in Table 1, four postmenopausal female subjects not on ERT had their blood levels evaluated for estrogen levels before and after use of the estrogen containing toothpaste. No adverse side effects were observed. The data suggest that there is adequate systemic absorption of estradiol that has the same beneficial effects as the orally ingested or transdermal estrogen in postmenopausal women not on ERT. The peak serum level of estradiol occured at one hour for all subjects tested. There was another peak of estradiol in 12 hours. This second peak was due to enterohepatic circulation of achieving estradiol. The blood estradiol levels remained elevated in 75% cases in 24 hours.

7.4 EXAMPLE 4

An Oral Dentrifice Composition Formulated as a Toothpaste

The oral dentrifice composition in the present example is formulated as toothpaste. Toothpaste compositions are prepared by mixing together in any order and by any conventional means the essential and optional components described herein. Once prepared, the compositions provide a pH of from about 4.0 to about 8.0, preferably 6.5 to 7.5, when the compositions are slurried with water in a 3:1 weight ratio of water to composition.

Fluoride toothpastes providing pH values within the 4.0 to 8.0 range provide especially effective dental enamel antisolubility benefits compared to toothpastes with pH values outside this range. Flavoring of toothpastes within this pH range is also readily accomplished.

The present example illustrates an oral dentrifice formulated as toothpaste especially designed for treating alveolar bone loss, solving the problem of tooth loss, as well as providing a treatment for hormonal imbalance and reducing the risk of cardiovascular and Alzheimer's diseases. Alveolar bone is the portion of the jawbone that supports the teeth. The treatment is used either in the short term, or in certain aspects for the remaining lifetime of the patient.

Compliance is improved using the oral dentrifice composition and method provided in this example because tooth brushing is routine for most individuals. Using oral dentifice compositions results in better compliance with estrogen replacement therapy with no adverse effects and equal safty and efficacy compared to other well tried compositions and methods of use. Because the estradiol is directly absorbed into the bloodstream, it has a rapid effect, and there is no gastric irritation as often occurs with ingestion of estradiol.

The toothpaste is prepared as described in previous examples and includes from about 0.25 mg to about 1 mg of estradiol per unit dose of toothpaste used. Through brushing the teeth once or twice daily, three times a week or only in the evenings, estrogen is absorbed through the buccal and gingival mucosa into the systemic circulation. The estradiol within the toothpaste acts on the estrogen receptors in the jawbone, preventing osteoporosis of the jawbone and the loss of teeth, and increasing alveolar bone mass density. Fluoride in the toothpaste enhances the effect of estrogen on the osteocytes containing estrogen receptors. Patients who have not had a hysterectomy are given about 2.5 mg of progesterone per day, in order to reduce the risk of uterine cancer.

..........*

All of the compositions and/or methods disclosed and claimed herein can be made and executed without undue experimentation in light of the present disclosure. While the compositions and methods of this invention have been described in terms of preferred embodiments, it will be apparent to those of skill in the art that variations may be applied to the compositions and/or methods, and in the steps or in the sequence of steps of the methods described herein, without departing from the concept, spirit and scope of the invention. More specifically, it will be apparent that certain agents that are both chemically and physiologically related may be substituted for the agents described herein while the same or similar results would be achieved. All such similar substitutes and modifications apparent to those skilled in the art are deemed to be within the spirit, scope and concept of the invention as defined by the appended claims.

8.0 REFERENCES

The following references, to the extent that they provide exemplary procedural or other details supplementary to those set forth herein, are specifically incorporated herein by reference.

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WHAT IS CLAIMED IS:

1. An oral dentrifice composition comprising a therapeutically effective amount of at least a first steroidal hormone or steroidal hormone derivative.

2. The oral dentrifice composition of claim 1, wherein said composition is formulated as a toothpaste, tooth powder, mouth and gum powder, dental cream, prophylaxis paste, mouthwash, mouthrinse, lipid oral gel, non-lipid oral gel, lozenge, chewing gum, dental tablet, foaming dental tablet or pastille.

3. The oral dentrifice composition of claim 1 or 2, wherein said composition further comprises at least a first abrasive agent, polishing agent, fluoride ion source, binder, humectant, surfactant, emulsifying agent, thickening agent, consistency regulating agent, chelating agent, gelling agent, sudsing agent, pellicle film penetrating agent, flavoring agent, sweetening agent, anticalculus agent, antiplaque agent, antigingivitis agent, pigment, coloring agent, antibacterial agent, whitening agent, preservative, stannous salt or water.

4. The oral dentrifice composition of any preceding claim, wherein said composition comprises at least a first fluoride ion source selected from the group consisting of sodium fluoride (NaF), stannous fluoride (SnF_2), potassium fluoride (KF), potassium stannous fluoride (SnF_2-KF), indium fluoride (InF_3), zinc fluoride (ZnF_2), ammonium fluoride (NH_4F) and stannous chlorofluoride (SnC1F).

5. The oral dentrifice composition of any preceding claim, wherein said composition comprises:

(a) at least a first binder selected from the group consisting of seaweed colloid, a cellulose derivative and a gum;

(b) an edible polyhydric alcohol humectant; or

(c) at least a first surfactant selected from the group consisting of an anionic surfactant, a betaine surfactant, a nonionic surfactant, a cationic surfactant, an amphoteric surfactant and a zwitterionic surfactant.

6. The oral dentrifice composition of any preceding claim, wherein said composition comprises at least a first testosterone or testosterone derivative.

7. The oral dentrifice composition of any preceding claim, wherein said composition comprises at least a first estrogen or estrogen derivative.

8. The oral dentrifice composition of claim 7, wherein said composition comprises at least a first estrogen or estrogen derivative selected from the group consisting of a conjugated estrogen, a conjugated estrogen derivative, an esterified estrogen, an esterified estrogen derivative, estradiol, an estradiol derivative, estrone, an estrone derivative, estriol and an estriol derivative.

9. The oral dentrifice composition of claim 7 or 8, wherein said composition further comprises at least a second steroidal hormone or steroidal hormone derivative selected from the group consisting of a progestin, a progestin derivative, a progesterone, a progesterone derivative, a progestogen, a progestogen derivative, testosterone and a testosterone derivative.

10. The oral dentrifice composition of any one of claims 7 through 9, wherein said composition comprises at least one estrogen or derivative thereof; at least one progestin, progestogen, progesterone, or derivative thereof; and at least one of testosterone or a derivative thereof.

11. The oral dentrifice composition of any one of claims 7 through 10, wherein said composition further comprises a therapeutically effective amount of at least a second, distinct antiosteoporosis agent.

12. The oral dentrifice composition of any one of claims 7 through 11, wherein said composition further comprises at least a second, distinct antiosteoporosis agent selected from the group consisting of a selective estrogen receptor modulator, alendronate, calcitonin, calcium, fluoride and vitamin D.

13. The oral dentrifice composition of any one of claims 7 through 12, wherein said composition further comprises a selective estrogen receptor modulator selected from the group consisting of tamoxifen and raloxifene.

14. The composition of any preceding claim, for use in therapy.

15. The composition of any preceding claim, for use in administering a steroidal hormone to a subject.

16. The composition of any preceding claim, for use in providing increased serum levels of a steroidal hormone to a subject.

17. The composition of any preceding claim, for use in treating a subject that has, or is at risk for developing, a condition that requires increased systemic levels of a steroidal hormone.

18. The composition of any one of claims 7 through 17, for use in treating a subject that has, or is at risk for developing, a condition associated with estrogen deficiency.

19. The composition of any one of claims 7 through 18, for use in treating a subject that has, or is at risk for developing, tooth loss, osteoporosis of the jaw bone or a condition characterized by a dentally localized estrogen deficiency.

20. The composition of any one of claims 7 through 19, for use in treating a subject that has, or is at risk for developing, systemic osteoporosis or decreased bone density.

21. The composition of any one of claims 7 through 20, for use in administering estrogen to a postmenopausal female or a female with premature menopause or a menopausal disorder.

22. Use of a composition in accordance with any preceding claim in therapy.

23. Use of a composition in accordance with any one of claims 1 through 21 in the manufacture of a medicament for treating or preventing a disease or disorder associated with a steroidal hormone deficiency.

24. Use of a composition in accordance with any one of claims 1 through 21 in the manufacture of a medicament for treating or preventing a disease or disorder associated with a systemic steroidal hormone deficiency.

25. Use of a composition in accordance with any one of claims 7 through 21 in the manufacture of a medicament for treating or preventing a disease or disorder associated with estrogen deficiency.

26. Use of a composition in accordance with any one of claims 7 through 21 in the manufacture of a medicament for treating or preventing tooth loss, osteoporosis of the jaw bone or a disease or disorder characterized by a dentally localized estrogen deficiency.

27. Use of a composition in accordance with any one of claims 7 through 21 in the manufacture of a medicament for treating or preventing systemic osteoporosis or decreased bone density.

28. Use of a composition in accordance with any one of claims 7 through 21 in the manufacture of a medicament for treating or preventing a disease or disorder associated with estrogen deficiency in postmenopausal women or women with premature menopause or a menopausal disorder.

29. A kit comprising, in at least a first suitable container, an oral dentrifice composition in accordance with any one of claims 1 through 21.

30. The kit of claim 29, wherein said oral dentrifice composition is formulated as a toothpaste and wherein said kit further comprises a toothbrush, mouthguard or mouthpiece for administering said toothpaste.

31. A method of providing a steroidal hormone to a subject, comprising administering to said subject an oral dentrifice composition in accordance with any one of claims 1 through 21.

32. The method of claim 31, wherein said oral dentrifice composition is formulated as a toothpaste and is administered to said subject by at least a first brushing of the teeth of said subject.

33. The method of claim 31 or 32, wherein said oral dentrifice composition is administered to said subject in an amount effective to provide therapeutically effective serum levels of said steroidal hormone in said subject.

34. The method of any one of claims 31 through 33, wherein said subject has, or is at risk for developing, a condition associated with testosterone deficiency and wherein said oral dentrifice composition comprises at least a first testosterone or testosterone derivative.

35. The method of any one of claims 31 through 33, wherein said subject has, or is at risk for developing, a condition associated with estrogen deficiency and wherein said oral dentrifice composition comprises at least a first estrogen or estrogen derivative.

36. The method of claim 35, wherein said subject has, or is at risk for developing, tooth loss, osteoporosis of the jaw bone or a condition characterized by a dentally localized estrogen deficiency.

37. The method of claim 35 or 36, wherein said subject has, or is at risk for developing, systemic osteoporosis or decreased bone density.

38. The method of any one of claims 35 through 37, wherein said oral dentrifice composition is administered to said subject in an amount comprising between about 0.25 mg and about 2.5 mg of said estrogen or estrogen derivative per unit dose.

39. The method of any one of claims 35 through 38, wherein said subject is a postmenopausal female or a female with premature menopause or a menopausal disorder.

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(54) Title: ORAL STEROIDAL HORMONE COMPOSITIONS AND METHODS OF USE

(57) Abstract: Provided are oral dentifrice compositions comprising a therapeutically effective amount of estrogen or an estrogen-containing substance. A variety of different methods of using the compositions, for example in the treatment or prevention of tooth loss or osteoporosis, are also provided. Additionally, therapeutic kits comprising one or more of the present compositions are provided.

INTERNATIONAL SEARCH REPORT

Interr nal Application No
PCT/US 00/12404

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K7/16

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB 2 058 564 A (HORTON J E;UPJOHN CO) 15 April 1981 (1981-04-15) the whole document	1-39
P,X	DE 198 32 169 A (JENAPHARM GMBH) 27 January 2000 (2000-01-27) the whole document	1-3,5,7, 8,14,15, 17-19, 22-26, 31,32,35
X	EP 0 345 039 A (AMER & COMPANY INC) 6 December 1989 (1989-12-06) claims; examples	1-3,5, 14,15, 19,23, 24,31,32

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 November 2000	30/11/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Couckuyt, P

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INTERNATIONAL SEARCH REPORT

Interr nal Application No
PCT/US 00/12404

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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X	EP 0 671 175 A (PROCTER & GAMBLE) 13 September 1995 (1995-09-13) page 3, line 26 - line 27; claim 1	1-3,14, 15,22
X	WO 94 16673 A (GILLETTE CO ;CAUSTON BRIAN EDWARD (GB)) 4 August 1994 (1994-08-04) page 13; example 19	1-3,14, 15,22
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